Novel Generation Strategies for Pyranosyl Nitrile Oxides and their use in *C*-Glycoside Synthesis

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In Memory of Gladys Baker
1907 – 2002

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16) RSC Postgraduate Industrial Tour, 3 Days, Sevenoaks – Poster presented
17) RSC Carbohydrate Group Spring Meeting, University of Warwick, 2000
18) RSC Carbohydrate Group Spring Meeting, University College Dublin, 2001 – Poster presented
19) RSC Carbohydrate Group Autumn Meeting, University of Reading, 2002, - Oral Presentation

Glossary of Terms, Symbols and Abbreviations

Ac	acetate
AIBN	azoisobutyronitrile
[α]	optical rotation
Ar	aromatic
Bz	benzoyl
Bn	benzyl
BuLi	butyllithium
cm	centimetre
δ	chemical shift
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAD	dimethyl acetylenedicarboxylate
DMAP	dimethylaminopyridine
DMF	N, N-dimethylformamide
DMSO	dimethylsulfoxide
ether	diethyl ether
equiv.	equivalent
FAB	fast atom bombardment
FMO	frontier molecular orbital
g	grams
HOMO	highest occupied molecular orbital
hr	hour
Hz	hertz
HRMS	high resolution mass spectroscopy
IR	infra-red
J	coupling constant
LDA	lithium diisopropylamide
lit.	literature
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	moles per litre
M^+	molecular ion

Me	methyl
mg	milligrams
MHz	mega hertz
min	minute
mmole	millimole
mp	melting point
m/z	mass to charge ratio
nd	not determined
NMNO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ppm	parts per million
q	quartet
s	singlet
t	triplet
TDI	tolyene-2, 4-diisocyanate
THF	tetrahydrofuran
t.l.c	thin layer chromatography
ν	wavelength

Abstract

Nitrile oxide chemistry has been investigated as a route to *C*-glycosides. This approach involves the generation and cycloaddition reactions of pyranosyl nitrile oxides with olefinic and acetylenic dipolarophiles, and manipulation of the resulting cycloadducts.

Three methods for the generation of pyranosyl nitrile oxide have been utilised: firstly isocyanate-induced dehydration of pyranosylnitromethanes (the Mukaiyama approach); secondly hypochlorite-mediated oxidation of pyranosyl aldoximes, and finally base-catalysed dehydrohalogenation of pyranosyl hydroximoyl chlorides. The pyranosyl aldoximes derived from D-mannose, D-glucose, D-xylose and L-fucose were synthesised *via* stannate (II) mediated reduction of the corresponding pyranosylnitromethane (80–90%), whilst direct chlorination of the aldoximes gave the hydroximoyl chlorides (80-95%).

The efficiency of nitrile oxide generation by all three methods was illustrated by the high yields of 3,4-(dipyranosyl)-1,2,5-oxadiazole-2-oxides (furoxans) obtained by dimerisation on generation in the absence of a dipolarophile. For example, 3,4-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole-2-oxide (**164**) was prepared from 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosylnitromethane (**122**) in a 90% yield. The D-glucose, D-xylose and L-fucose derived analogues were synthesised in high yields (79 – 96%) utilising all three methods.

Where compatible, the Mukaiyama approach gave cycloadducts in good yields (>75%) (e.g. on reaction with methylenecyclohexane and styrene). However, for low boiling or thermally unstable dipolarophiles or for dipolarophiles with functional groups incompatible with the isocyanate dehydrating agent (e.g. dimethyl acetylenedicarboxylate, allyl alcohol), cycloadditions were carried out successfully using pyranosyl aldoximes and pyranosyl hydroximoyl chlorides as precursors. The cycloaddition reactions with achiral alkenes proceeded with low levels of diastereoselectivity (d.e. < 10%), in contrast to the cycloaddition of chiral alkenes where significant π-facial selectivity was observed (d.e. 40-80%).

The chemistry of the dipyranosyl furoxans has also been investigated. Hydrogenation of 3,4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-furoxan (**178**) in the presence of Raney nickel yielded the corresponding dipyranosyl-1,2-dioxime (**191**) in 77% yield. Preliminary studies

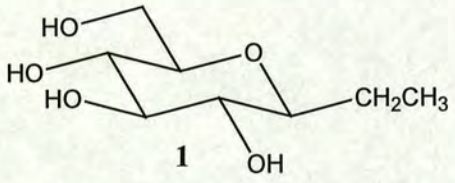
of the chemistry of this class of dioxime have been carried out, for example dehydration to the 1,2,5-oxadiazole (furazan) and re-oxidation to the dipyranosyl furoxan. Attempts at complexation of these novel chiral ligands with nickel show promising results.

Attempts to functionalise the 4-position of the isoxazoline ring by treatment with base (e.g. BuLi, LDA), followed by addition of an electrophile, led to the unexpected formation of glycals. For example, reaction of 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-isopropyl-β-D-mannopyranosyl)-2-isoxazoline (**155**) with BuLi afforded 5-(Spirocyclohexyl)-3-(4,6-*O*-isopropylidine-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**200**) in a 94% yield. The proposed mechanism involves deprotonation of the anomeric position, followed by elimination and hydrolysis of the resulting hemiketal.

Tables of Contents

1 Introduction

The work presented in this thesis involves the development of a novel route to carbon-linked glycosides (*C*-glycosides). *C*-glycosides, e.g. (**1**), are analogous to glycosides, e.g. (**2**), but with the exo-glycoside oxygen replaced by carbon. The approach used makes use of nitrile oxide / isoxazoline chemistry with particular emphasis on methods of nitrile oxide generation and their subsequent 1,3-dipolar cycloaddition reactions. The introduction is in three parts. Firstly, a brief overview of nitrile oxide and isoxazoline chemistry is given. In the second section the interest in *C*-glycosides and their potential applications is discussed, and finally the principal literature routes to *C*-glycosides are surveyed.



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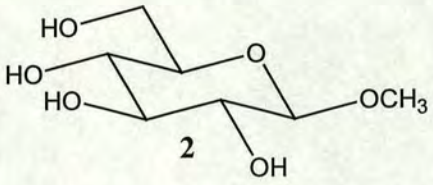

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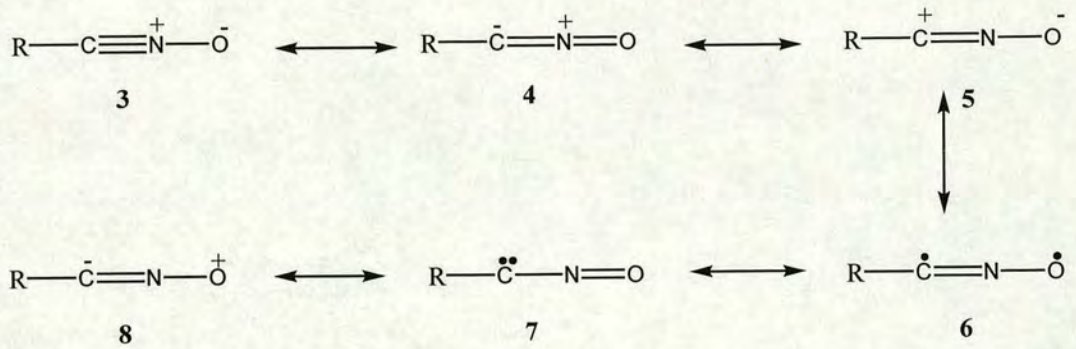
1.1 Nitrile oxide chemistry

1.1.1 Background

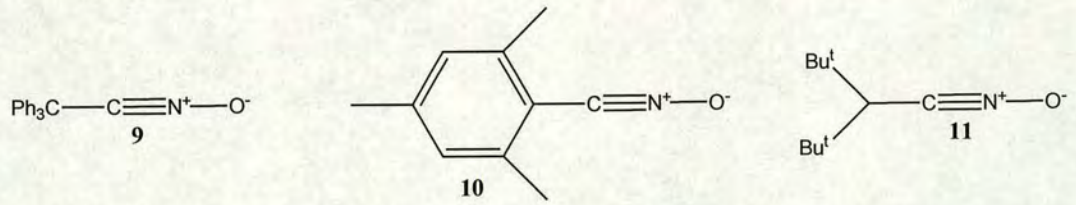
Nitrile oxides belong to the family of 1,3-dipoles. The chemistry of 1,3-dipoles, first classified by Huisgen[1], is vast and has been comprehensively reviewed in the two volume monograph entitled '1,3-Dipolar Cycloadditions' edited by Padwa.[2] Nitrile oxides, in their own right, are much researched and have been shown to be valuable tools in a wide range of synthesis, from natural products to polymer chemistry. Only a brief overview of their chemistry will be given here. More detailed discussion can be found in 'The Nitrile Oxides' by Grundmann and Grünanger,[3] 'Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis' by Torssell[4] and in the review 'Recent Advances in Synthetic Applications of Nitrile Oxide Cycloadditions' by Kanemasa and Tsuge.[5]

Nitrile oxides belong to the nitrilium betaine class of 1,3-dipoles. They are usually represented by a zwitterionic octet structure (**3**). However, they are more accurately described as a hybrid of the possible resonance forms (**3**)-(**8**) (Scheme 1).



Scheme 1

Most nitrile oxides are transient species which dimerise to 1,2,5-oxadiazole 2-oxides (furoxans), although there are a few examples of isolable nitrile oxides such as (**9**)[6], (**10**)[7] and (**11**)[8] which are resistant to dimerisation, an effect attributable to steric factors. For synthetic purposes, nitrile oxides are therefore generated *in situ* in the presence of the dipolarophile.

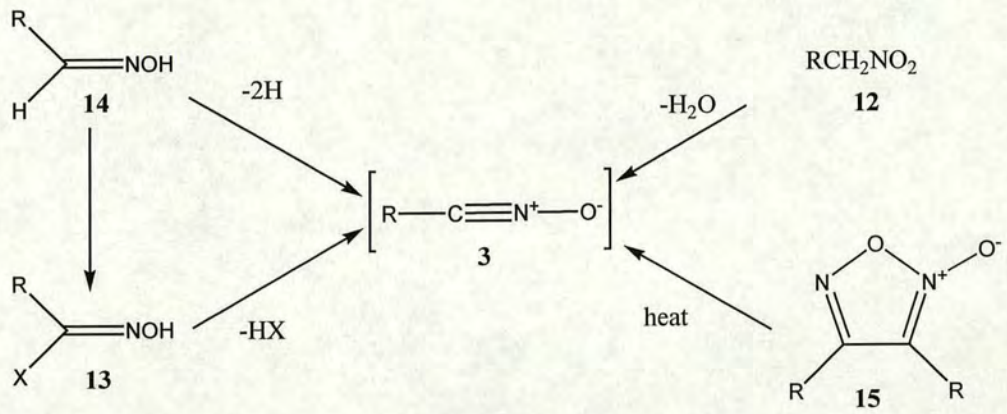


1.1.2 Generation of nitrile oxides

There are four common precursors to nitrile oxides (**3**). These are outlined in Scheme 2. A popular entry point to nitrile oxides is the Mukaiyama[9] dehydration of primary nitro compounds (**12**) using an isocyanate as dehydrating agent and a catalytic amount of base. Alternative dehydrating agents have been reported including acid chlorides,[10] anhydrides,[11] phosphorous oxychloride,[12] *p*-toluenesulfonic acid,[13] and *di-tert*-butyl dicarbonate.[14] An alternative route involves the dehydrohalogenation of hydroximoyl halides (**13**), commonly carried out by treatment with base, usually triethylamine,[15] or potassium fluoride.[16] Thermal generation is also possible by heating in an inert solvent.[17,18] The conversion of aldoximes (**14**) to nitrile oxides is another common strategy. The reaction often involves *in situ* synthesis of the hydroximoyl halides using alkaline sodium hypochlorite,[19] but other reagents such as iodosylbenzene[20] and trichloroisocyanuric acid[21] have been employed. Often the

aldoxime is converted to the hydroximoyl chloride using chlorine gas[22] or milder methods such as NCS,[23] followed by base-catalysed dehydrohalogenation. Direct dehydrogenation for *syn* aldoximes using lead tetraacetate[24] has also been reported.

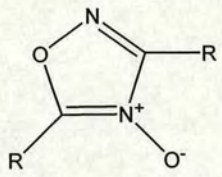
A less common route to nitrile oxides is thermal cycloreversion of the furoxan dimers (**15**).[25] This often requires temperatures greater than 200 °C. However, for ring strained furoxans (e.g. trimethylenefuroxan[26]) and furoxans with bulky substituents, such as di-*t*-butyl(2-trimethylsilyloxyprop-2-yl)furoxan, cycloreversion is more facile taking place at 120 - 165°C.[27]



Scheme 2

1.1.3 Reactions of nitrile oxides

Nitrile oxides undergo a wide variety of reactions, as outlined in Scheme 3. In the absence of other reactants nitrile oxides tend to dimerise to furoxans.[3] These furoxans can also be observed as by-products in cycloaddition reactions. Alternative dimers, 1,2,4-oxadiazole 4-oxides[28] (**16**) and 1,4,2,5-dioxadiazines[29] (**17**) are occasionally observed. For example, generation of benzonitrile oxide in the presence of pyridine or boron triflouride affords 3,6-diphenyl-1,4,2,5-dioxadiazine.[29]



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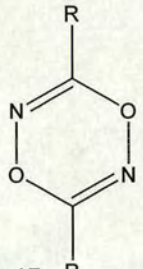

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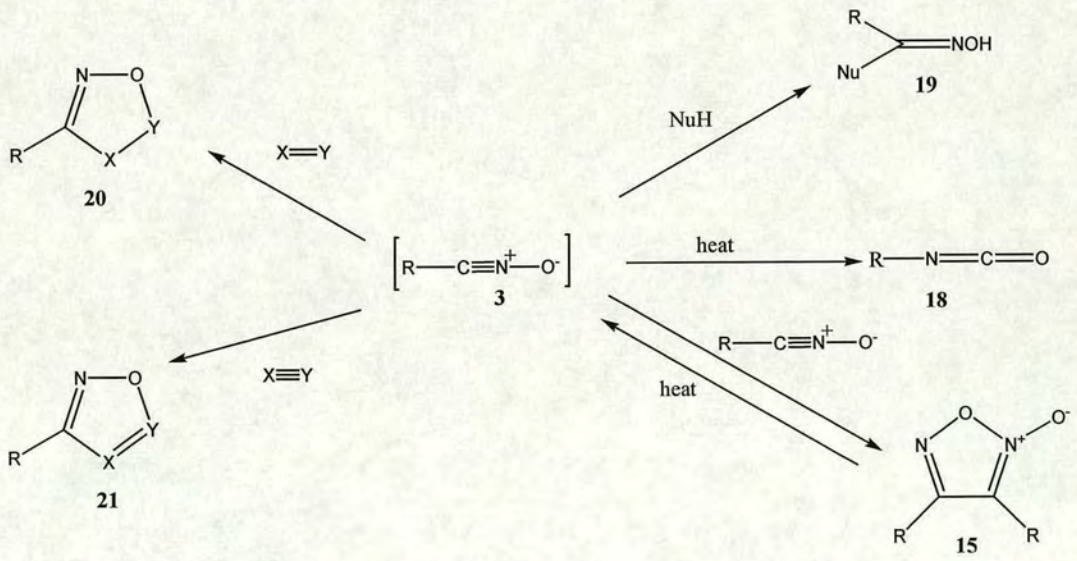
More stable nitrile oxides may undergo thermal rearrangement at temperatures greater than 110°C to give isocyanates (**18**). For example, heating benzonitrile oxide in xylene quickly to 110°C causes partial conversion to phenyl isocyanate with diphenylfuroxan as the major product.[30]

The nitrile oxide can undergo 1,3-additions with nucleophiles to yield substituted oximes (**19**). Appropriate nucleophiles include thiols,[31] alcohols[32], amines[33] and more recently organometallic species such as Grignard reagents.[34]

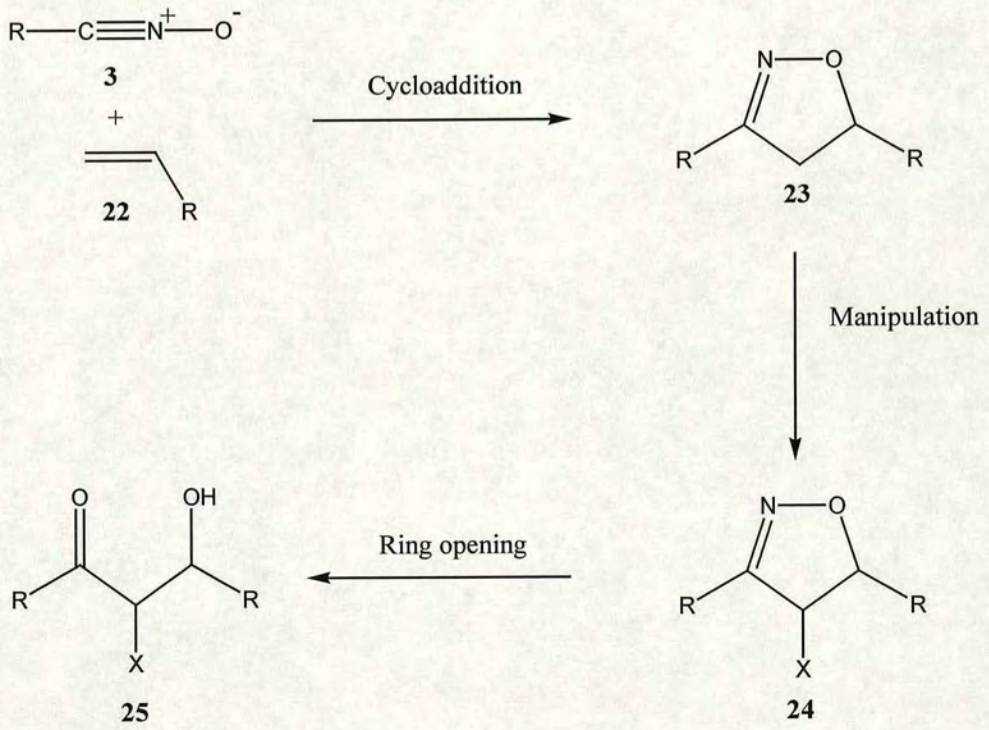
The most important synthetic application of nitrile oxides are their 1,3-dipolar cycloaddition reactions with unsaturated system, i.e. double (C=C, C=N, C=S, C=O) and triple (C≡C, C≡N) bonds to give 5-membered heterocyclic compounds (**20**), (**21**) incorporating the C=N-O unit.



Scheme 3

1.2 Synthetic applications of nitrile oxide / isoxazoline chemistry.

The 1,3-dipolar cycloaddition reaction is a valuable route to 5-membered heterocycles. Of particular synthetic interest is the 1,3-dipolar cycloaddition of nitrile oxides with alkenes and alkynes to give 2-isoxazolines and isoxazoles respectively. This interest lies in the fact that these heterocycles contain masked functionalities which can be released at various points in the synthetic route. Thus, the nitrile oxide / isoxazoline route has been applied to a wide range of synthetic challenges such as natural product synthesis.[35] The strategy involves three key steps. The first is the cycloaddition step, followed by modification of the isoxazoline (**23**) ring prior to the final step, ring cleavage. This is illustrated in Scheme 4 for β-hydroxyketones (**25**).



Scheme 4

1.2.1 Cycloadditions of nitrile oxides to alkenes

The first stage of the nitrile oxide / isoxazoline approach involves the cycloaddition of the nitrile oxide with an alkene. The steric outcome of the reaction depends on the nature of the dipolarophile. Alkenes which are mono-substituted or 1,1-disubstituted normally react regiospecifically to give 5-substituted adducts. This is not the case, however, when a strongly electron withdrawing group is attached to the alkene when a mixture of 5- and 4-substituted products are seen. 1,2-Disubstituted alkenes show much less regiospecificity, whilst more functionalised alkenes often prove to be much less reactive.

The origin of the regioselectivity effects can be rationalised by frontier molecular orbital (FMO) theory.[36] The formation of the transition state is brought about by interaction of the FMO's, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reactants. The interaction of the FMO's for dipoles and dipolarophiles have been classified by Sustmann[37] into three groups. For dipolarophiles with conjugating (C) or electron donating (D) groups the dominant interaction is Sustmann type III between the HOMO of the dipolarophile and the LUMO of the dipole (Figure 1).

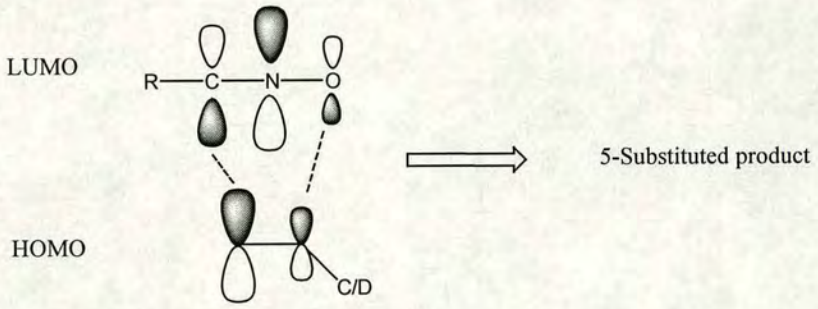


Figure 1

However, the introduction of an electron withdrawing group (W) lowers the energy of both the HOMO and the LUMO of the dipolarophile. Thus, Sustmann type II, interaction of the LUMO-dipolarophile, HOMO-dipole, is now possible and the 4-substituted product is seen (Figure 2).

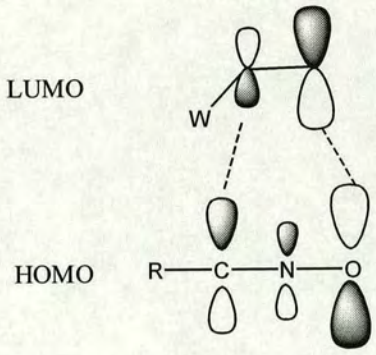
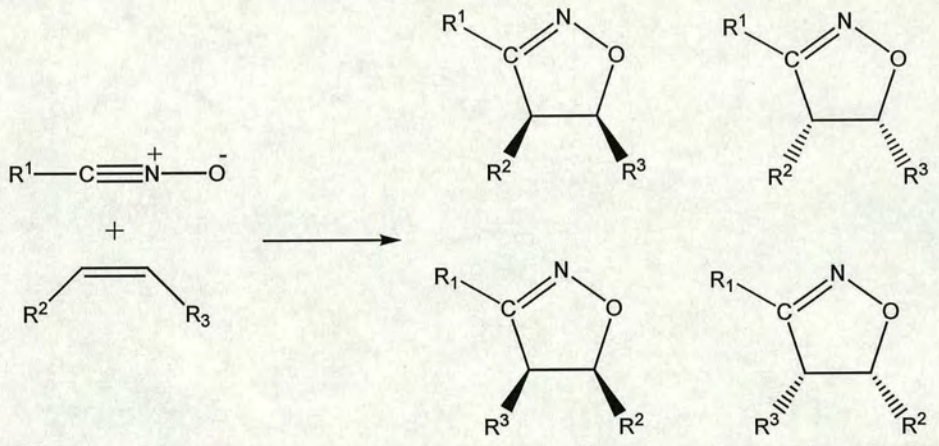


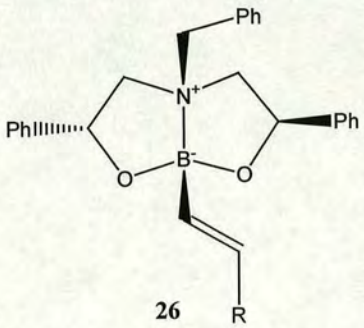
Figure 2

Cycloaddition reactions are believed to be a concerted[38] process and proceed with the retention of the dipolarophile stereochemistry. Thus, for a dipolarophile with two faces open to attack, two stereoisomers for each regiosiomer are obtained (Scheme 5).



Scheme 5

The control of absolute stereochemistry in 1,3-dipolar cycloadditions is becoming an increasing area of interest.[39] The most frequently applied strategy is the use of chiral auxiliaries either attached to the alkene, e.g. (**26**)[40] or less frequently to the dipole.[39] Investigation of the effect of microwave technology is also taking place.[41] Stereoselectivity can also be inferred by the stereochemistry of the reactants (e.g. chiral alkenes).[42]



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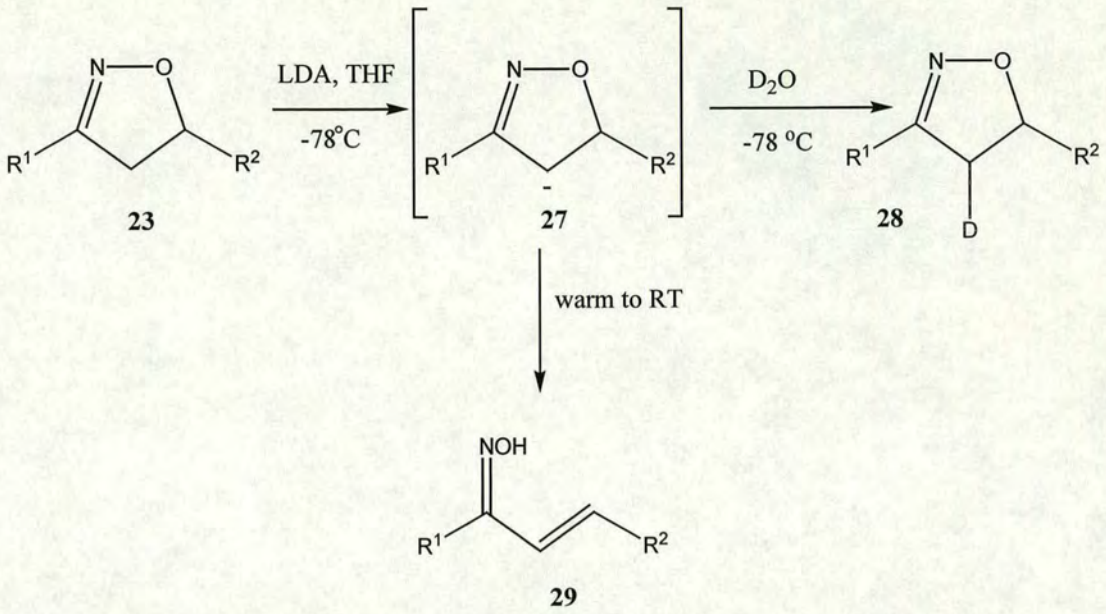
Kanemasa *et al*[43] have documented important effects of Mg(II) on the course of the nitrile oxide cycloaddition of benzonitrile oxide with an allylic alkoxide. The effects described include increased rate of cycloaddition and a stabilisation of the reactive nitrile oxide by coordination of the magnesium ion to the Lewis basic oxygen. More importantly it is reported that for the cycloaddition with chiral allylic alcohols significant syn-stereoselectivity (99:1 syn:anti) is observed. These observations have been applied to cycloadditions in natural product synthesis.[44]

1.2.2 Modification of the isoxazoline ring

The synthetic utility of isoxazolines is increased by their ability to undergo substitution reactions prior to ring opening (Scheme 6). Jäger *et al*[45, 46] have developed methods for substituting the 4-position of the isoxazoline ring. This involves treatment with a strong base, lithium di-isopropylamide (LDA) or butyllithium (BuLi) at -78°C followed by the trapping of the carbanion (**27**) with an electrophile to give the substituted isoxazoline (**28**). A variety of electrophiles have been used and the stereochemistry of the reaction investigated.[45] If the carbanion is left to warm to room temperature in the absence of an electrophile ring opening to the α,β-unsaturated oxime (**29**) can occur.



Scheme 6

1.2.3 Ring Opening

Cleavage of the N-O bond of the heterocycle releases a variety of fuctionalities depending on the conditions used (Scheme 7).[47] Commonly, hydrogenolysis using a hydrogenation catalyst such as Pd/C or Raney nickel[47] in aqueous conditions is employed to give the synthetically important β-hydroxyketone (**31**). Alternative methods of ring opening include treatment with titanium trichloride,[48] molybdenum hexacarbonyl,[49] ozone[50] and samarium iodide.[51] This strategy offers an alternative to the aldol condensation and indeed has some advantages. Problems such as cross and self aldol reactions, reversibility and non-selective enolate formation are less applicable to the isoxazoline route. The two routes also differ in which C-C bond is created as illustrated in Figure 3.

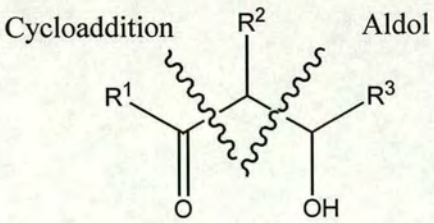
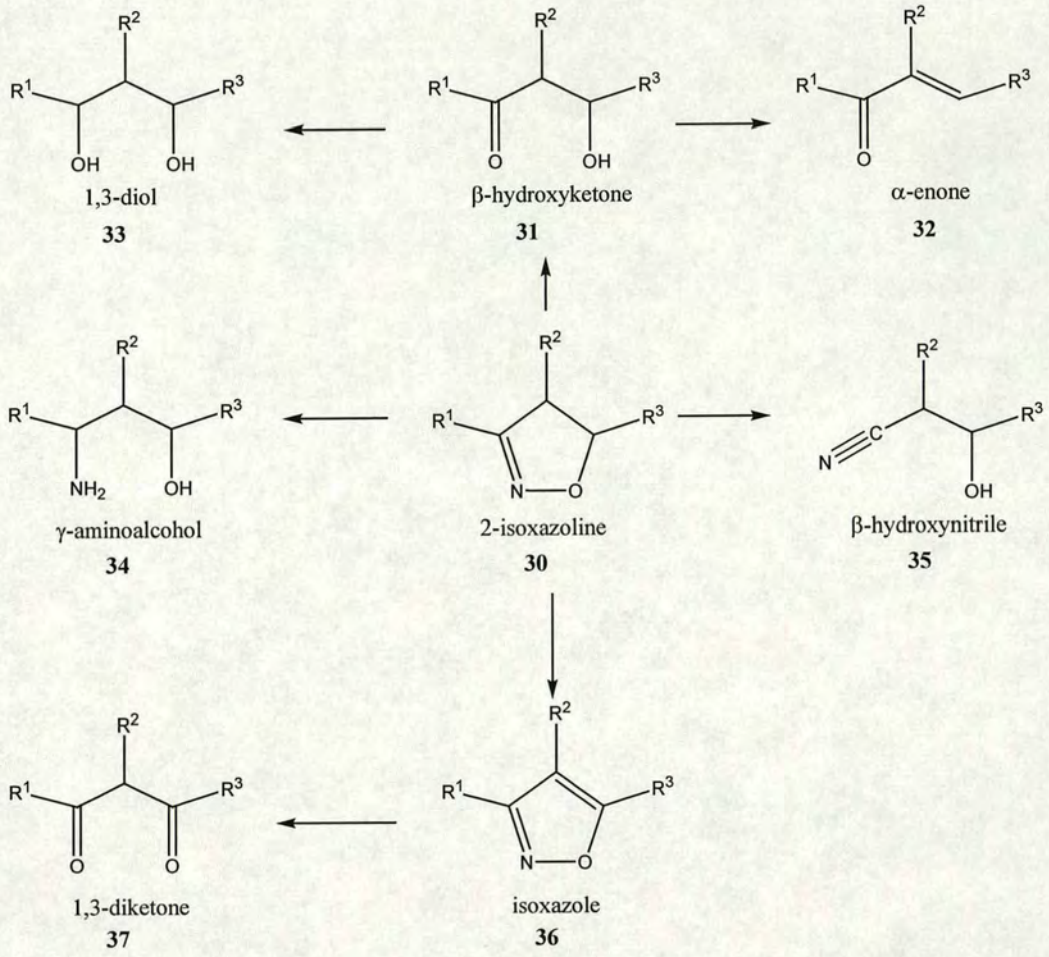


Figure 3



Scheme 7

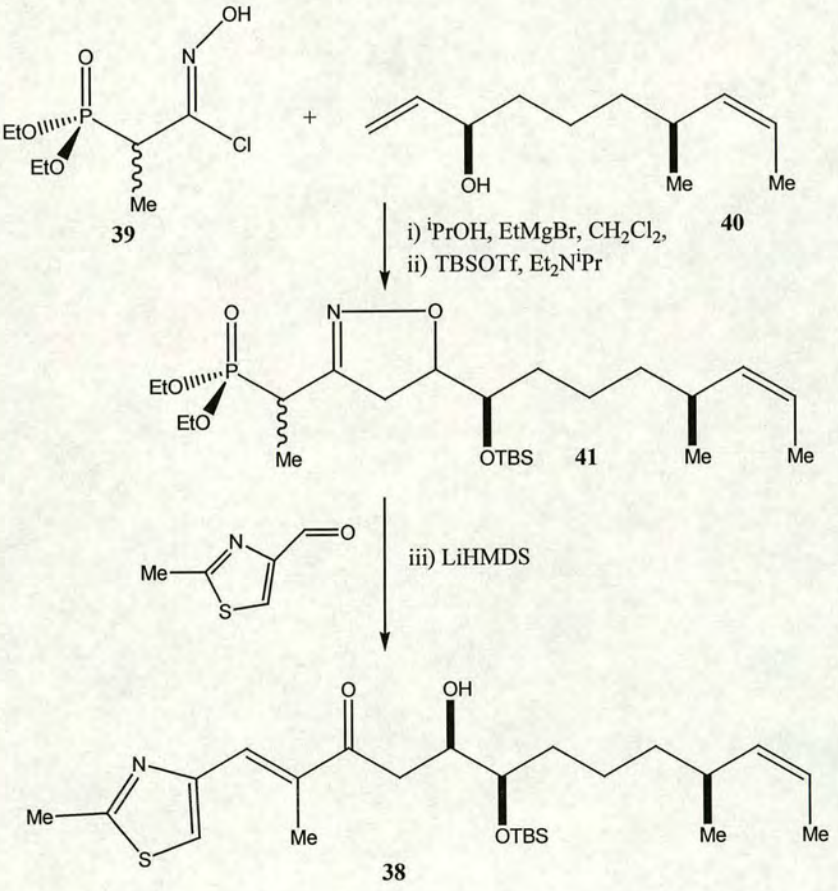
The β-hydroxyketone provides access to the α-enone (**32**) *via* dehydration and the 1,3-diol (**33**) by reduction. An alternative product, the γ-aminoalcohol (**34**) can be obtained by ring cleavage under non-aqueous conditions[52] using lithium aluminium hydride ($LiAlH_4$)[53] or hydrogenation with a catalyst. Jäger *et al*[53] have developed a stereoselective route to γ-aminoalcohols using $LiAlH_4$, although the diastereoselectivity observed is heavily dependant on the substituents present on the isoxazoline ring. β-Hydroxy nitrile (**35**) can be obtained by base deprotonation of 3-unsubstituted isoxazolines[54] or thermal decarboxylation[55] of isoxazoline-3-carboxylic acids.

The isoxazoline can also be oxidised to isoxazole (**36**) using a variety of reagents[56] including iodine.[57] Isoxazoles can alternatively be obtained by the cycloaddition reaction of nitrile

oxides with alkynes. As with isoxazolines, isoxazoles contain masked functionalities including 1,3-diketones (**37**) and β-keto nitriles.[57]

1.2.4 Examples of synthetic applications of nitrile oxide / isoxazoline chemistry

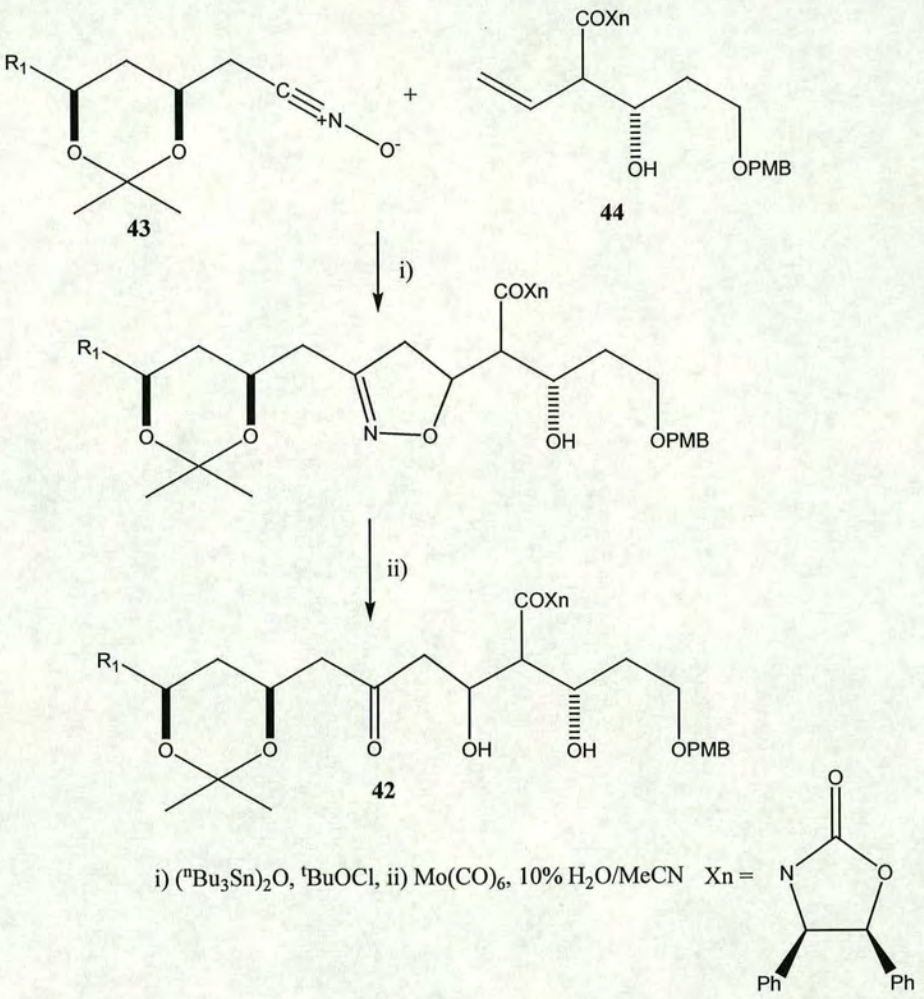
The synthetic potential of 2-isoxazolines has been exploited in the synthesis of a wide range of natural products and their analogues.[58] Recently, Carreira and co-workers[59] have used this approach to synthesise building blocks for polyketide-derived natural products. A specific example is the epothilone class of natural products,[44] which have similar properties as Taxol. The key component in the synthesis (**38**) was created by the stereospecific reaction of (**39**) and allylic alcohol (**40**) using the conditions reported by Kanemasa,[43] discussed previously, followed by a Wadsworth-Emmons coupling as outlined in scheme 8.



Scheme 8

Another example is reported by McGarvey and co-workers in their synthesis of the heptaene and pseudoheptaene subfamily of the polyene macrolide antibiotics.[60] This class of compound has gained prominence as consequence of their clinically important antifungal

activity. The key intermediate, the amphotericin polyol segment (**42**), was created by the cycloaddition of (**43**) and (**44**) and subsequent ring opening of the resultant isoxazoline (Scheme 9).



Scheme 9

The nitrile oxide / isoxazoline approach has also been applied to macrocycle synthesis,[61] carbohydrate chemistry,[62] alkaloids,[63] and amino acids.[64]

Research is currently underway investigating the application of nitrile oxide chemistry on the solid phase as it is believed to offer a number of advantages including the easy removal of dimerisation side products.[65, 66, 67]

1.3 Glycosidase inhibition

1.3.1 Introduction

Carbohydrates play a critical role in biological events such as intracellular communication and cell-mediated processes. These events are often controlled by glycosidases and glycosyltransferases and thus inhibition of these enzymes may find therapeutic applications in the treatment of various diseases. With this goal in mind much research is taking place into finding possible inhibitors. The dominant strategy involves the use of mimicry. Most success has been found with alkaloids but *C*-glycoside chemistry also shows promise.

1.3.2 Glycosidases - Mechanism of hydrolysis

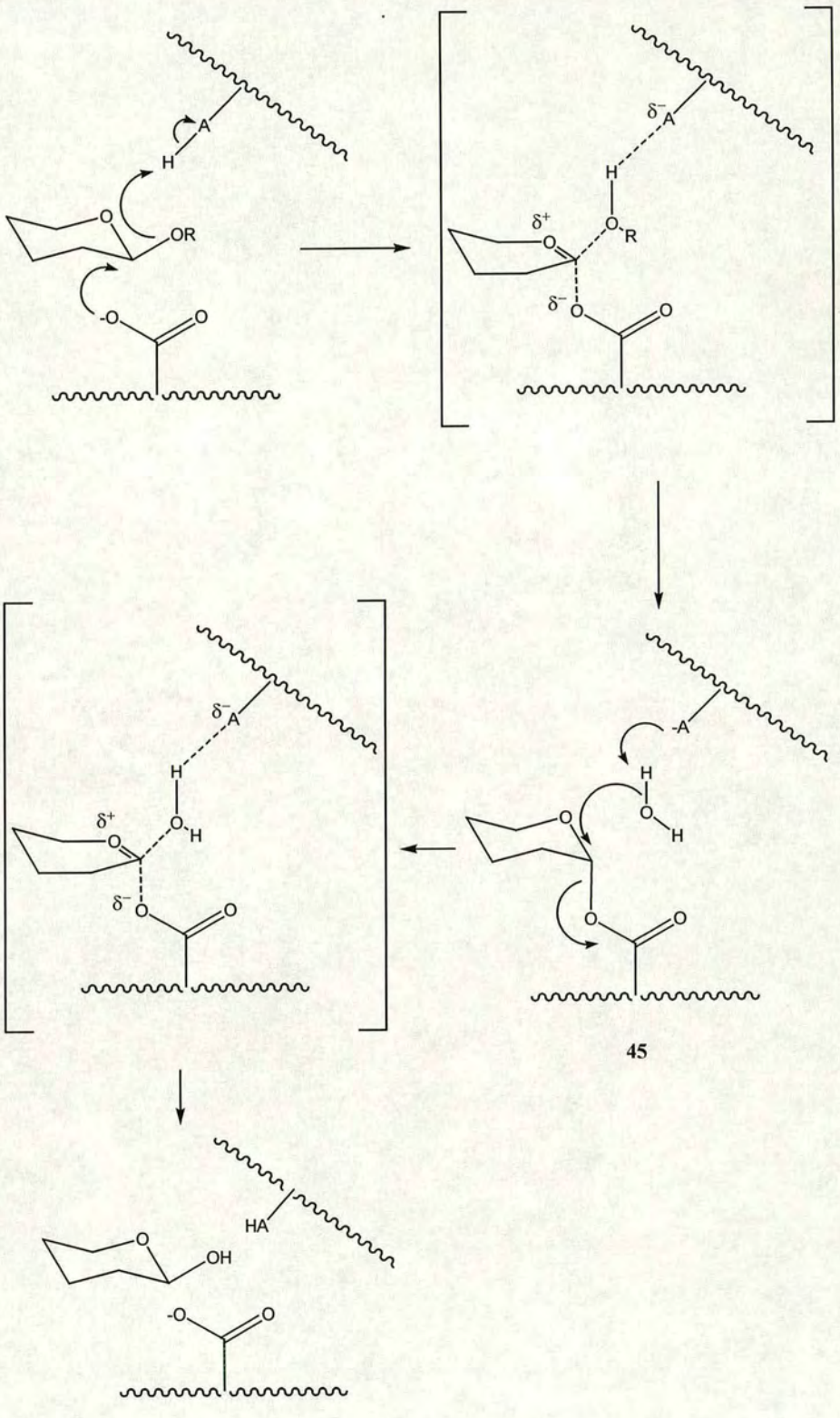
The hydrolysis of glycosidic linkages in most carbohydrate-containing molecules in nature are carried out by glycoside hydrolases (glycosidases). The classification[68] of these enzymes is based on several criteria:

i) the anomeric configuration of the substrate

ii) whether the configuration at the anomeric position is retained upon hydrolysis

iii) if the substrate is a pyranose or furanose ring

The mode of action can be considered as nucleophilic substitution at the saturated carbon of the anomeric centre. An important categorisation of glycosidases is whether there is retention or inversion of the anomeric centre. The mechanisms[69] for both were proposed by Koshland, with retention of configuration being explained by a three step double displacement (Scheme 10). The first step involves protonation of the glycosidic oxygen by an enzyme acid catalyst group, followed by displacement of the glycone by an enzyme bound carboxylate anion to form a covalently bonded intermediate (**45**). Finally, the carboxylate group is displaced by attack of water. Both of these stages involve cation-like transition sates.



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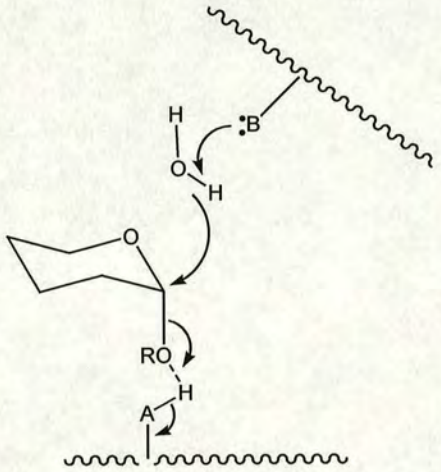
Scheme 10:

Inverting glycosidases invoke a single displacement mechanism involving protonation of the glycosidic oxygen followed by displacement of the glycone by attack of water (Scheme 11). The reaction proceeds through a glycosyl cation-like transition state. Unlike the double displacement mechanism, no covalently bound intermediate is formed.

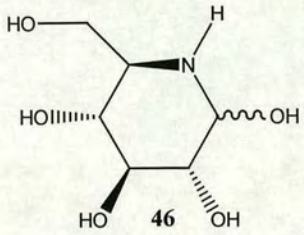


Scheme 11

1.3.3 Glycosidase inhibitors

The possible therapeutic application of glycosidase inhibitors has led to the synthesis of compounds with the potential to act as inhibitors. A number of inhibitors have also been isolated from Nature. In depth reviews of this area have been published by Elbein,[70] Winchester[71, 72] and Fleet[73], so only a brief survey will be shown here.

Alkaloids[70-73] that mimic the structure of monosaccharides are now believed to be widespread in plants and micro-organisms, and these sugar mimics inhibit glycosidases due to their structural resemblance to the sugar moiety of the natural substrate. These compounds contain nitrogen in the ring instead of oxygen and can be classified into five structural classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and notropanes. One of the first glycosidase inhibitors discovered was the polyhydroxylated piperidine, nojirimycin[74] (**46**).



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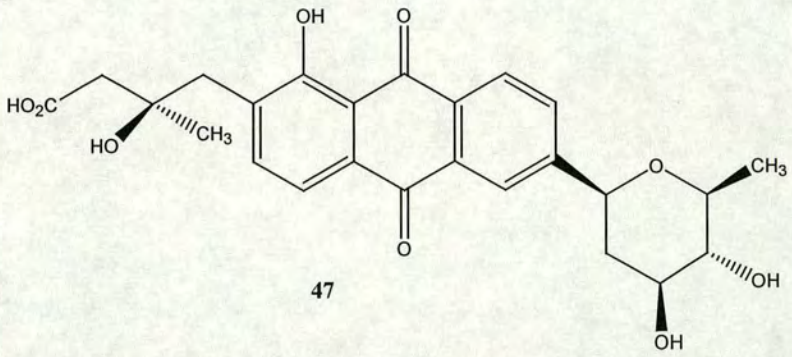
Another class of compound, which has shown promising inhibitory properties, are *C*-glycosides. These mimic *O*-glycosides by replacing the exoglycosidic oxygen with carbon. *C*-glycosides have been found in nature, for example the aryl *C*-glycoside vineomycinone B_2[75] (**47**). A subclass of *C*-glycosides are *C*-disaccharides where two sugar rings are linked *via* a carbon bridge instead of oxygen. These are often found as subunits of macromolecules such as palytoxin.[76] A related class are *C*-nucleosides in which the usual C-N bond of nucleosides is replaced by a C-C bond, e.g. pseudouridine (**48**).



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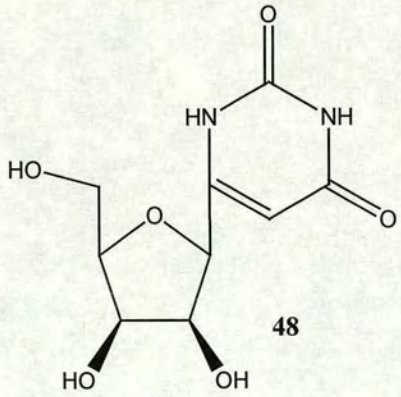

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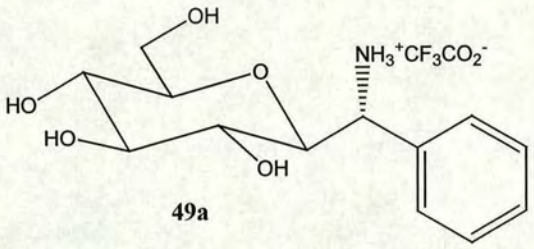
All three classes have been shown to display inhibitory qualities. Schmidt *et al*[77] have synthesised a diastereomeric pair of amino substituted β-benzyl-*C*-glycosides which show inhibition of β-glucosidase from sweet almonds. It is interesting to note that (**49a**) has a similar activity to 1-deoxynojirimycin, whilst (**49b**) has an activity two orders of magnitude lower.



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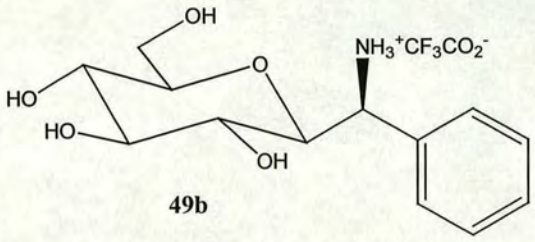

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1.3.4 Mode of action of glycosidase inhibitors.

The good inhibitory qualities of the alkaloid compounds has been attributed to their ability to mimic the cation-like transition state.[78] This is indicated by the pH dependency of the inhibition. At physiological pH, the ring nitrogen is protonated and thus mimics the oxycarbenium ion-like transition state (Figure 4).

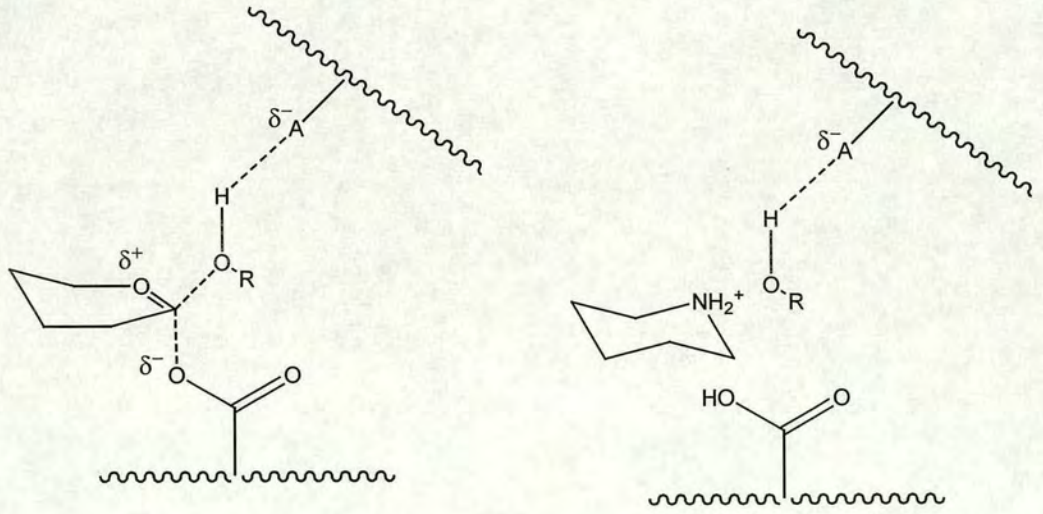


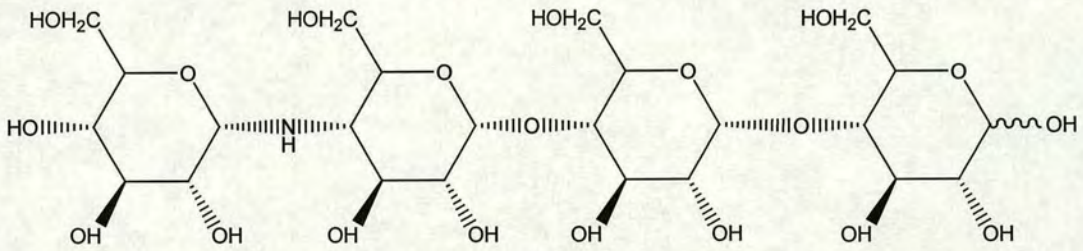
Figure 4

1.4 Applications of glycosidase inhibitors

Glycosidases are involved in a wide range of important biological processes. The potential to modify these processes by inhibition of the glycosidases has possible cell biological and therapeutic applications. Winchester and Fleet[72] have reviewed the biomedical and biotechnological applications of glycosidase-inhibiting mimics, so only a brief summary will be given here.

1.4.1 Diabetes and anti-obesity

Digestive glycosidases found in the cell membrane of the small intestine are oligo- and disaccharidases. These enzymes digest dietary carbohydrate to monosaccharides which are absorbed through the intestinal wall. Inhibition of all or some of these activities could regulate the absorption of carbohydrate with possibility for application in the treatment of diabetes and obesity. Acarbose[79] (**50**) was introduced by Bayer in 1990 for the treatment of diabetes.



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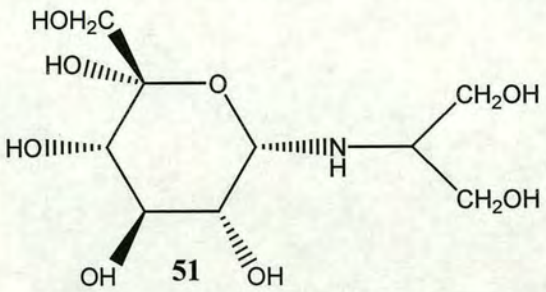
The treatment of obesity may be possible using the sucrase / maltase inhibitor AO-128[80] (**51**) which has been shown to reduce fat accumulation in the abdominal cavity, which is associated with circulatory difficulties.



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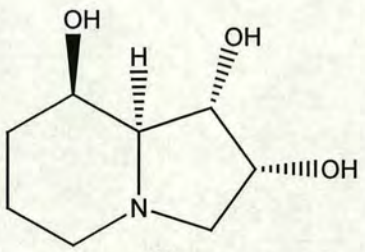
Other therapies for diabetes may come from inhibition of lysosomal[73] and processing glycosidases.[73]

1.4.2 Treatment of cancer

There is growing evidence that carbohydrate residues on cell-surface glycoconjugates play an important role in the metastatic spread of tumours. Metastasis is the process by which cancer cells invade the blood vessels or lymphatic system and are transported round the body to set up secondary tumours. The prevention of these secondary tumours is of great importance in the treatment of cancer. Cancerous cells are known to be more heavily glycosylated than normal and it is believed that this is linked to metastasis.[81] The use of glycosidase-inhibiting sugar mimics to prevent the formation of *N*-linked oligosaccharides associated with cancer cells and to inhibit the catabolic glycosidases that trim these surface glycoconjugates is being actively pursued as a therapeutic strategy for cancer. Swainsonine[82] (**52**) has shown dramatic inhibition of melanoma cell colonisation in mice whilst castanospermine[83] (**53**) has been shown to exhibit antimetastatic activity by inhibiting platelet aggregation of metastatic cells as well as reducing adhesion of tumour cells to the vascular endothelium.



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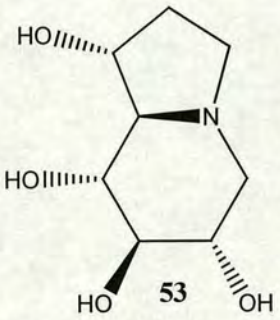

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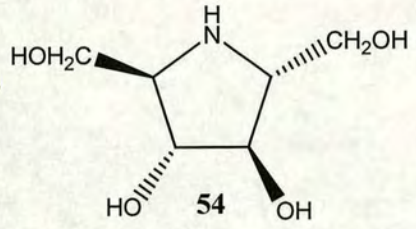
1.4.3 Antiviral activity

Many animal viruses contain an outer envelope, which is composed of one or more viral glycoprotein. These are often essential proteins that are required in the viral life cycle, either in virion assembly and secretion and/or infectivity. As processing of these glycoproteins occurs through the cellular machinery, processing glycosidase inhibitors have been used to study the role of the *N*-linked oligosachharides in several viral systems. α-Glucosidase

inhibitors such as castanospermine[84] (**53**) are potent inhibitors of HIV replication and thus may have a role to play in the treatment of this condition.

1.4.4 Insect antifeedants

The use of glycosidase inhibitors as selective insecticides is being investigated in the agrochemical industry. The inhibition of intestinal disaccharidases are known to have toxic effects on specific insect species. For example, (2R,5R)-bis(dihydroxymethyl)-(3R,4R)-dihydroxypyrrolidine[85] (DMDP) (**54**) has exhibited selective toxicity for certain species of caterpillar.



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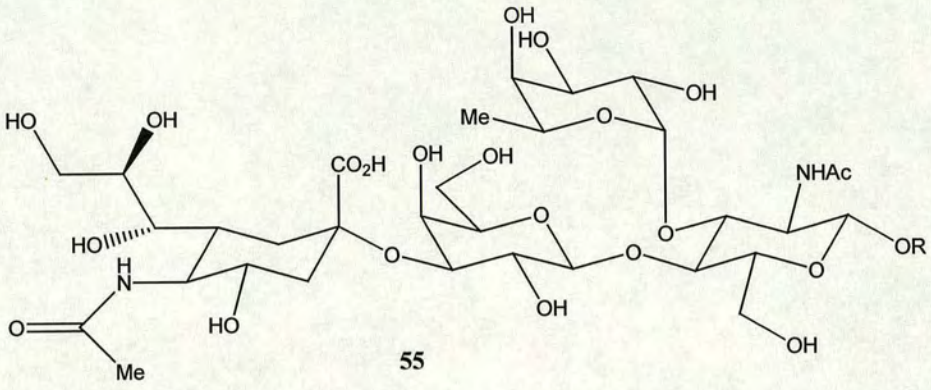
Amino-sugar compounds have been used to deter insects from feeding, therefore offering possible applications in crop protection. Castanospermine[85] (**44**) and DMDP[86] (**51**) have both been found to act as locust antifeedants.

1.5 Other carbohydrate based therapeutics

As well as glycosidase inhibition, other possible carbohydrate therapeutics are under investigation with possible applications in the treatment of various disease states. The binding of sialyl Lewis X (**55**) to selectins is believed to play an important role in inflammatory reponses.[87] Thus, it is hoped that low molecular weight sialyl Lewis X mimics may counteract excess inflammation. As yet no drug has reached the market but a number are in clinical trial.



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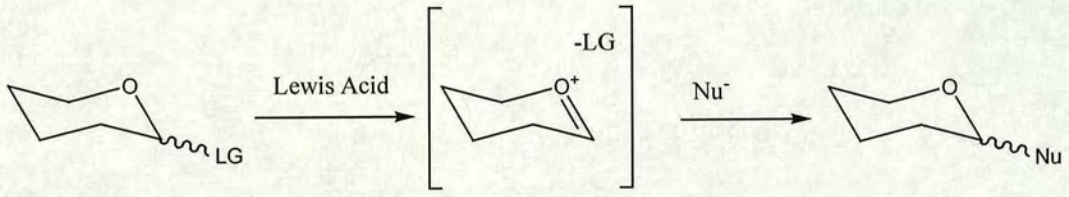
The first carbohydrate-based drug to find widespread application in humans was the glycosylaminoglycan heparin,[88] which has been used in the treatment of thrombosis since 1937. Heparin increases the activity of antithrombin III, which suppresses enzymes that promote coagulation. A number of low-molecular weight heparins, which have greater bioavailability, are currently on the market.

1.6 Synthesis of *C*-glycosides

With the realisation that *C*-glycosides have potential therapeutic applications and also with their stability to enzymic degradation *in vivo* making them excellent candidates for examining carbohydrate-protein interactions, a wide range of synthetic strategies for *C*-glycoside synthesis have been adopted. The first synthesis was reported in 1950 by Hurd *et al*[89] and involved reaction of various Grignard reagents with tetra-*O*-acetyl glucopyranosyl chloride. A vast array of different approaches to *C*-glycosides has been reported since then and a number of reviews of the area are available.[90-92] Thus, only a brief overview of the area will be given here.

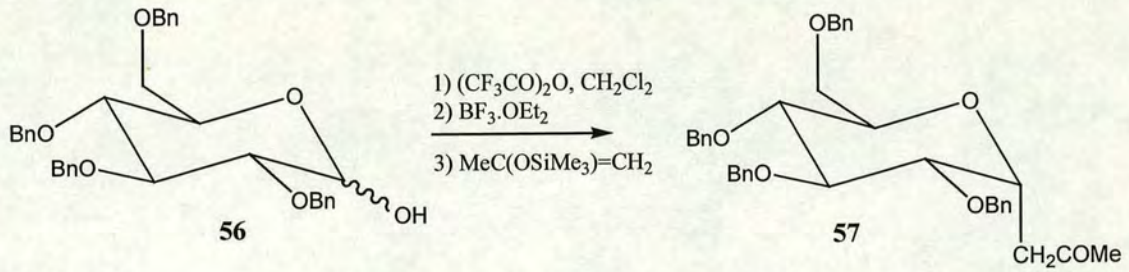
1.6.1 Electrophilic sugars in *C*-glycoside synthesis

The most common method for carbon-carbon bond formation at the anomeric carbon involves nucleophilic attack on this electrophilic centre (Scheme 12). A wide range of leaving groups have been employed such as carboxylate and halides in conjunction with various nucleophiles, including organometallic reagents. The reaction is often mediated by a Lewis acid.



Scheme 12

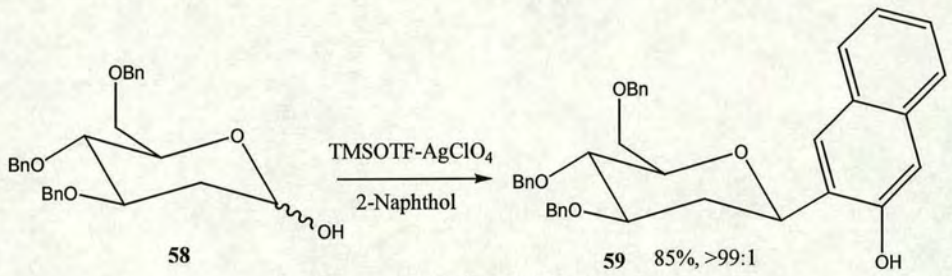
Allevi *et al*[93] have reported the reaction of silyl enol ethers with glucose derivatives (**56**) to give *C*-glycosides (**57**) as shown in Scheme 13.



Scheme 13

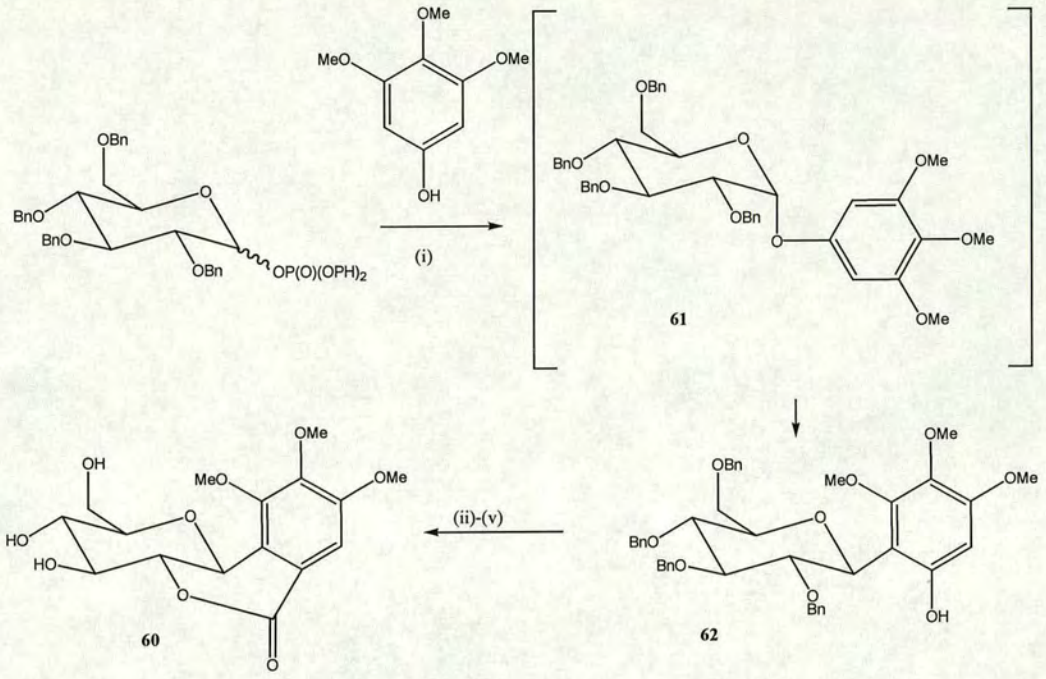
1.6.2 Rearrangement reactions

The electrophilic nature of the anomeric position is utilised in the synthesis of aromatic *C*-glycosides *via* O→C rearrangements. This approach has been used by Toshima *et al*[94] (Scheme 14). They found that treatment of the protected sugar (**58**) with a Lewis acid and 2-naphthol gave the *O*-glycoside, which rearranged to the *C*-glycoside (**59**). Good yields were obtained for a range of sugars with high stereoselectivity observed (β:α ratio up to 99:1).



Scheme 14

Recently, Seeberger and co-workers[95] have used this rearrangement methodology to synthesise the naturally occurring *C*-glycoside, bergenin (**60**). This compound has been found in extracts of *Macaranga peltata* used in Indian folk medicine. This short and simple synthetic approach involves the synthesis of the *O*-glycoside (**61**) which rearranges to the *C*-glycoside (**62**). Palladium catalysed carbonylation followed by deprotection and lactonisation gave the final product in a 33% overall yield (Scheme 15).

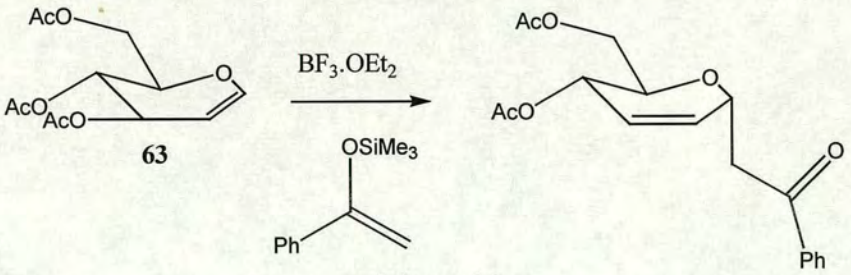


i) TMSOTf, CH_2Cl_2,-20°C - RT, ii) Tf_2O, Lutidine, DMAP, iii) CO, $Pd(OAc)_2$, KOAc, DMSO, iv) H_2, $Pd(OH)_2$, MeOH, v) MeOH, $SOCl_2$

Scheme 15

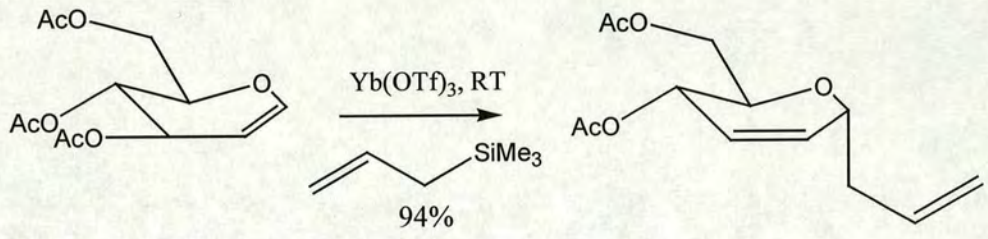
1.6.3 Glycals

Glycals have been extensively used in the synthesis of *C*-glycosides. One of the original examples was reported by Fraser-Reid and Dawe[96] in which they examined the reaction of tri-*O*-acetyl glucal (**63**) using a variety of different conditions. They found the optimum conditions to involve $BF_3.OEt_2$ as Lewis acid with the reaction carried out at -40°C (Scheme 16).



Scheme 16

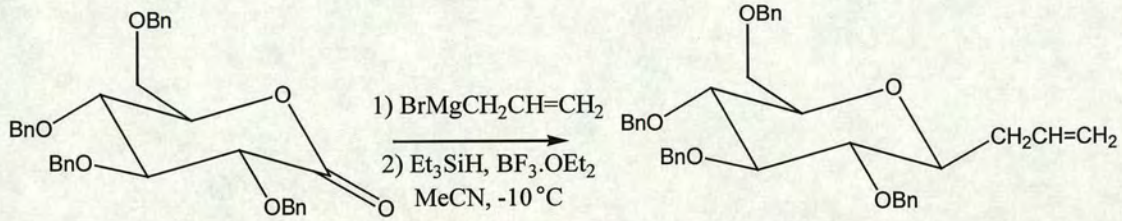
In an attempt to increase yields and stereoselectivities, various Lewis acid activators have been investigated. Recently, Schmidt *et al*,[97] have reported a highly stereoselective synthesis of *C*-pseudoglycals using $Yb(OTf)_3$ as catalyst (Scheme 17).



Scheme 17

1.6.4 Carbonyl addition reactions

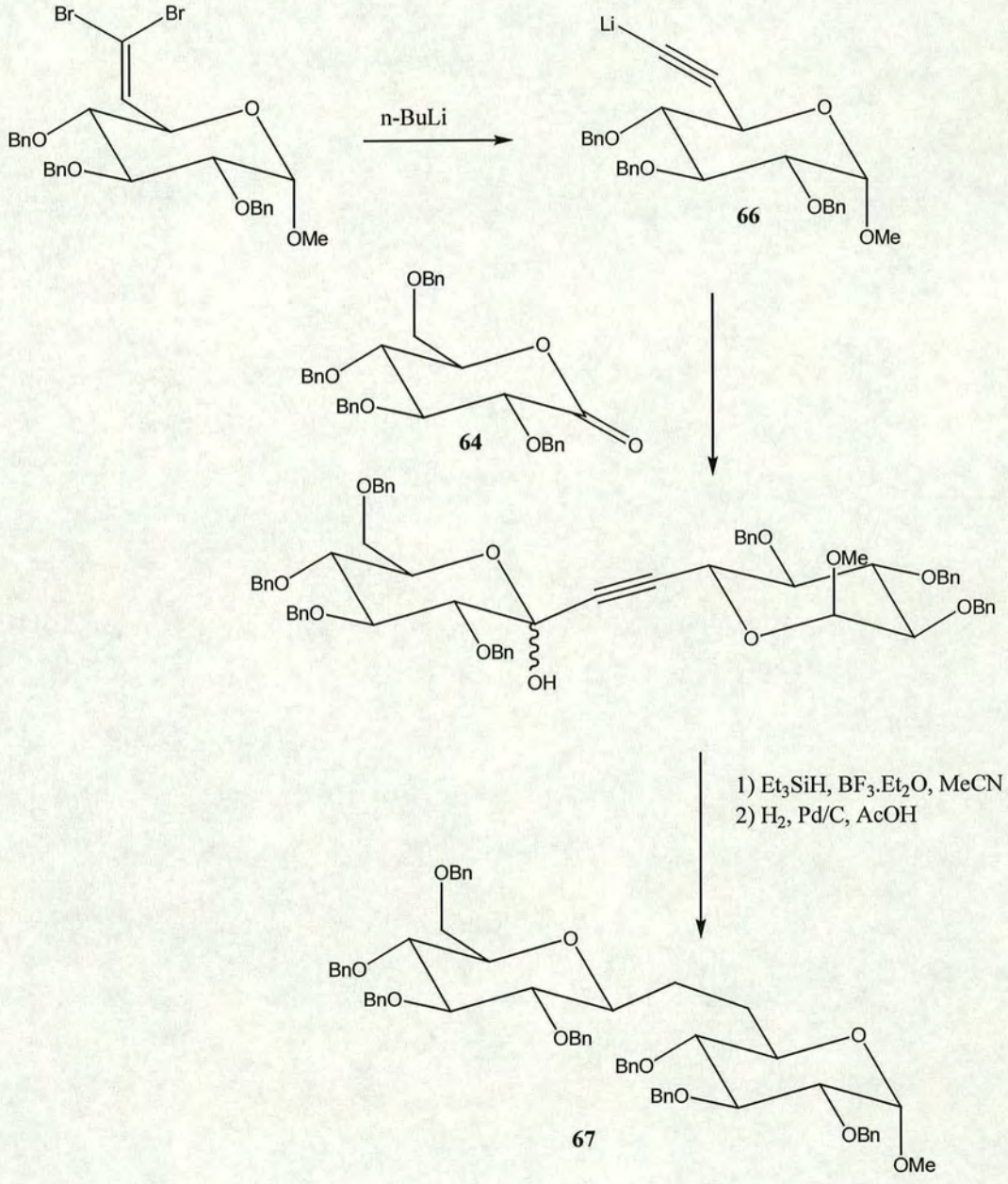
The electrophilic natures of sugar lactones and formyl *C*-glycosides have been utilised in the synthesis of *C*-glycosides. The synthesis of *C*-glycosides from sugar lactones usually involves the addition of an organometallic reagent and this has proved a reliable method for the synthesis of β-*C*-glycosides. Much of the work in this area was pioneered by Kishi *et al*.[98] Treatment of the sugar lactone (**64**) with either an allyl Grignard or a lithio ester, followed by selective reduction with triethylsilane gave β-allyl-*C*-glycoside (**65**) (Scheme 18).



64 **65**

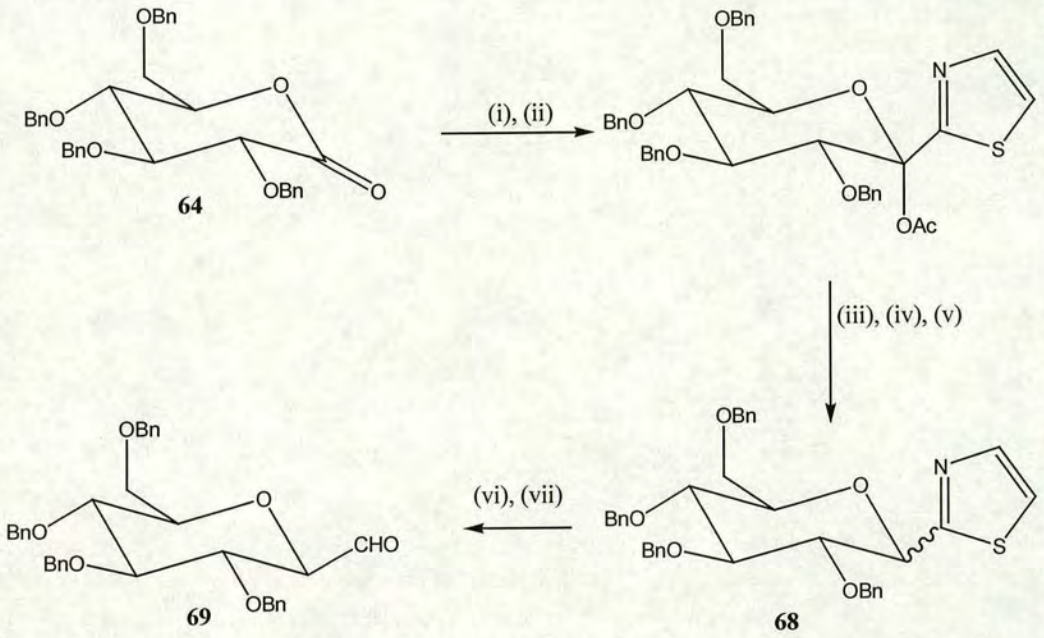
Scheme 18

The first synthesis of a *C*-disaccharide, reported by Sinaÿ and Rouzad,[99] involved the addition of an anionic sugar species (**66**) to a sugar lactone (**64**) to give a β-(1→6')-*C*-disaccharide (**67**) (Scheme 19). This methodology has been extended by Sinaÿ[100] to the synthesis of *C*-oligosaccharides.



Scheme 19

Dondoni and co-workers[101] have utilised sugar lactones (**64**) as a route to formyl *C*-glycosides by reaction with 2-lithiothiazole (Scheme 19). Acetylation of the resultant anomeric hydroxyl followed by removal of the ester and finally cleavage of the thiazole ring (**68**) yields the desired formyl *C*-glycoside (**69**). Dondoni[102] has utilised (**69**) as a building block for the preparation of more elaborate *C*-glycosides (see section 1.6.5).

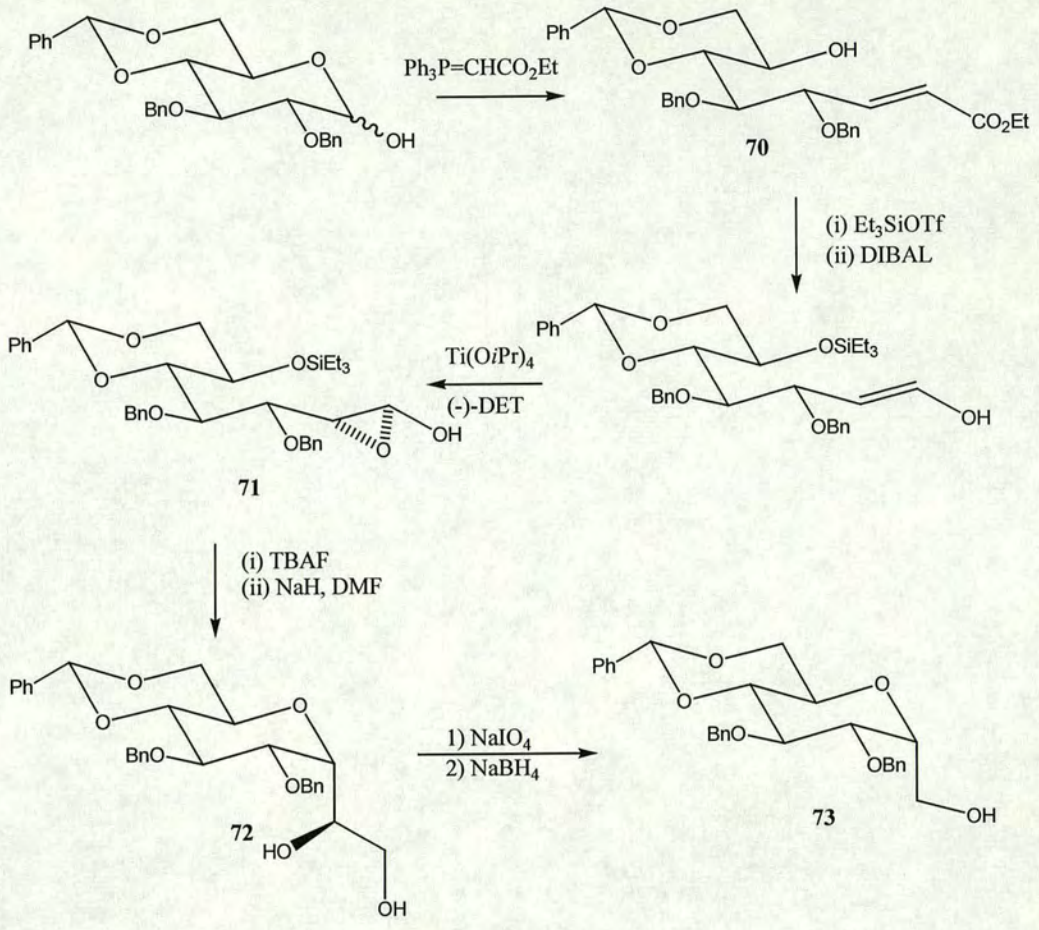


(i) 2-lithiothiazole, (ii) Ac_2O, (iii) Et_3SiH, TMSOTf, RT, MeCN, (iv) MeCN, MeOTf, (v) $NaBH_4$, (vi) $HgCl_2$-H_2O, (vii)*i*-PrOH, Et_3N

Scheme 20

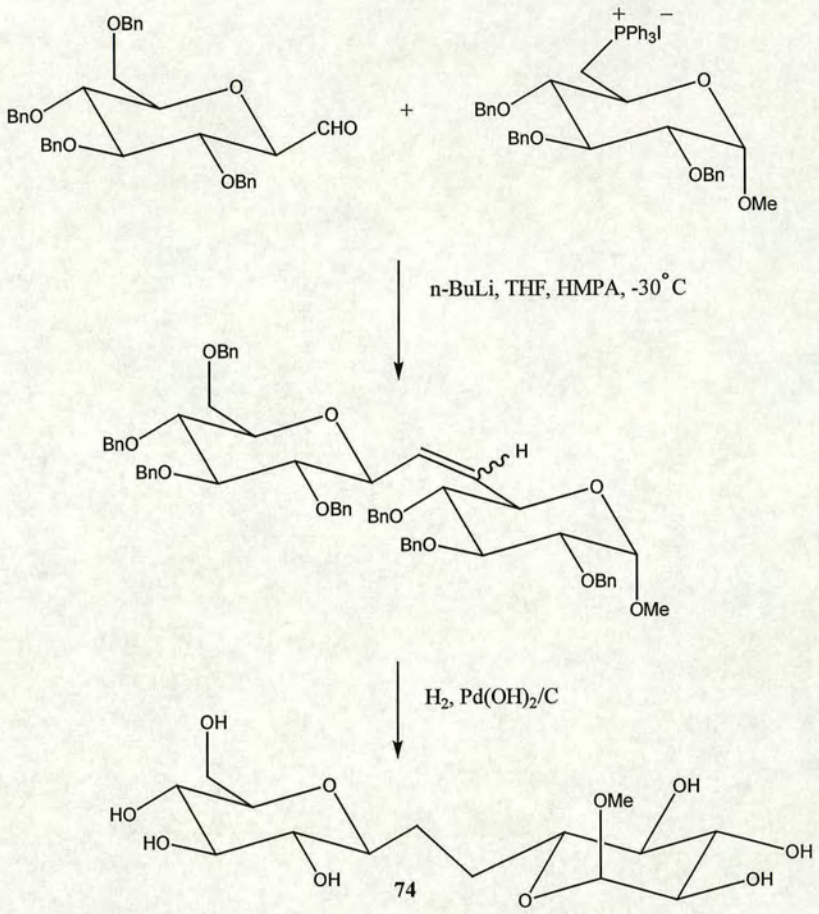
1.6.5 Wittig approach

Wittig reactions have been widely used for the synthesis of *C*-glycosides. In the 1980's Masamune, Sharpless and co-workers[103] reported the use of asymmetric epoxidation to gain both α- and β-*C*-glycosides from an open chain Wittig product (Scheme 21), for example the α-hydroxymethyl compound (**73**). Standard Wittig conditions gave the open chain derivative (**70**). Following protection of the free hydroxyl group and hydrolysis of the ester, epoxidation was achieved using the Sharpless conditions to give both isomers (**71**) depending on the chirality of the catalyst. Desilylation caused cyclisation to the *C*-glycoside (**72**). Periodate cleavage followed by reduction of the aldehyde formed gave the desired *C*-glycoside (**73**).



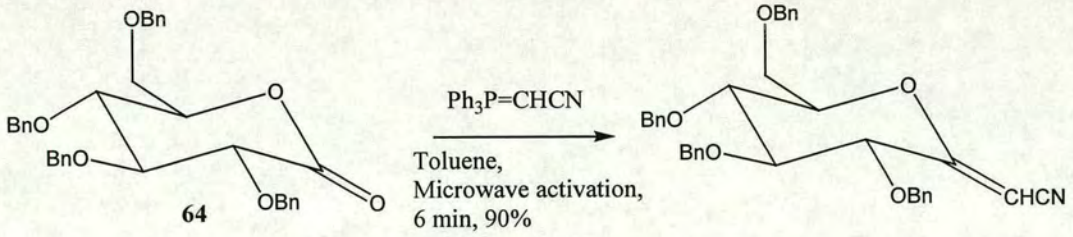
Scheme 21

Dondoni and co-workers[102] have utilised their formyl *C*-glycoside to form a number of α- and β-(1→6')-*C*-disaccharides by reaction with a sugar derived phosphate ester. The example shown in Scheme 22 is methyl *C*-gentiobioside (**74**).



Scheme 22

More recently, Chapleur *et al*[104] have described a Wittig olefination on a sugar derived lactone (Scheme 23). The reaction involves treatment of the lactone (**64**) with cyanomethyl triphenylphosphorane, prepared from the commercially available phosphonium chloride. The use of microwave activation dramatically reduced the length of reaction time from 16 hours in refluxing toluene to under 10 minutes.



Scheme 23

1.6.6 Anomeric carbanions

The normal electrophilic character of the anomeric centre has been reversed by a number of groups to produce nucleophilic sugars (Figure 5). This is often aided by the presence of a stabilising group at the anomeric position such as a nitro, ester or sulfur based functional group.

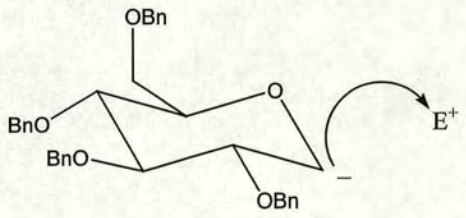
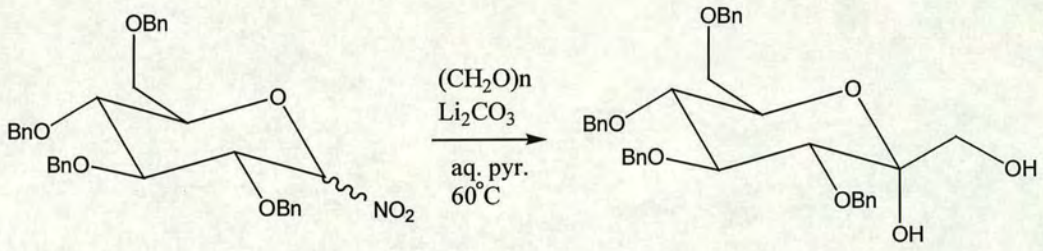


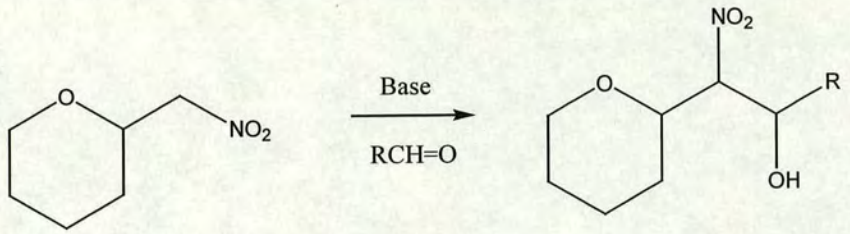
Figure 5

One of the most commonly used stabilising groups is the nitro group and much of the work in this area has been pioneered by Vasella and co-workers[105] (Scheme 24).



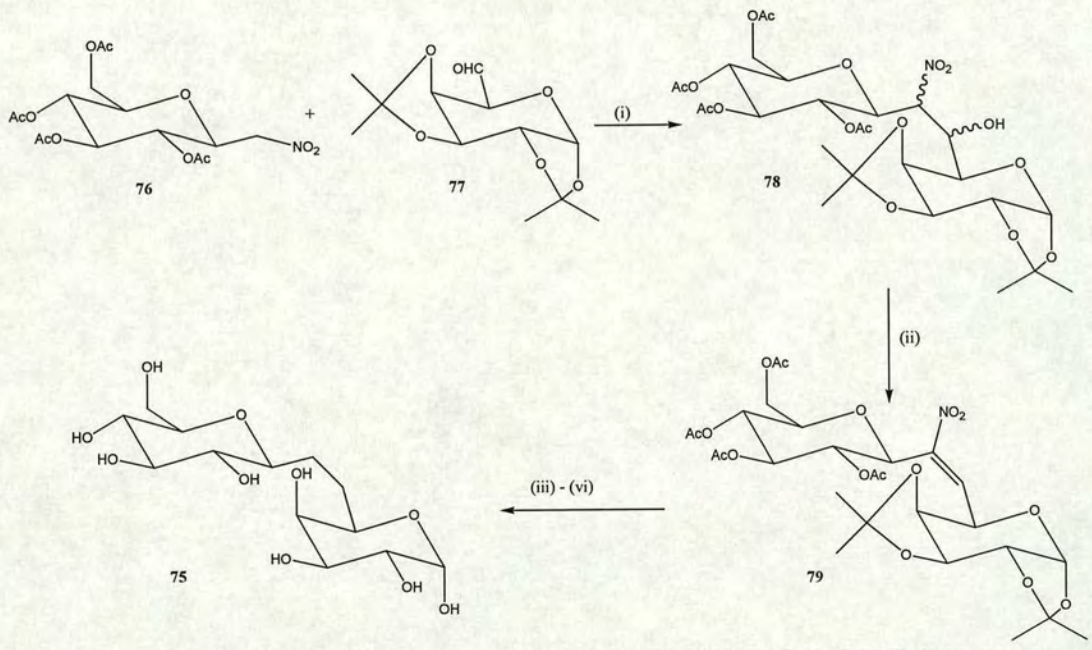
Scheme 24

A variation on this theme is the use of pyranosylnitromethanes in *C*-glycoside synthesis. This involves generation of an anion on the exocyclic carbon α- to the anomeric position (Scheme 25) and its subsequent use in a nitroaldol reaction. Pyranosylnitromethanes have been synthesised in two steps from the parent sugar by a number of groups including Köll and co-workers,[106] and they have proved to be valuable precursors to other *C*-glycosides.



Scheme 25

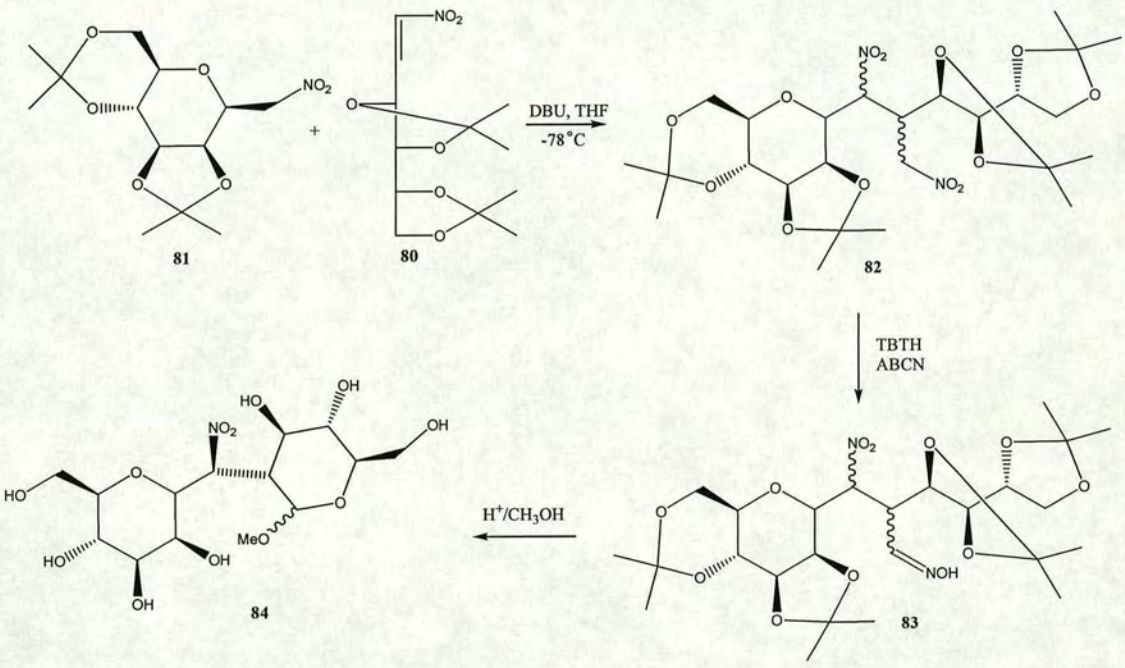
Martin and Lai[107] used the nitroaldol reaction (Scheme 26) in the synthesis of the D-Glc-*C*-β-(1→6)-D-Gal derivative (**75**). Reaction of the pyranosylnitromethane (**76**) with aldehyde (**77**) gave the adduct (**78**) as a mixture of diastereomers. The nitroaldol product was converted to the nitroalkene (**79**) by elimination of acetic acid, and subsequent reduction, radical denitration and deacetylation gave the required β-(1→6)-linked *C*-disaccharide (**75**). Formyl *C*-glycosides, such as those synthesised by Dondoni,[101] have been utilised by Bednarski *et al*[109] in nitroaldol reactions to form *C*-disaccharides.



(i) KF, CH_3CN, 18-crown-6; (ii) Ac_2O, Pyridine; (iii) $NaBH_4$; (iv) Bu_3SnH, AIBN, Heat; (v) NaOMe, MeOH; (vi) Amberlite IR-120 (H^+), H_2O, Heat

Scheme 26

More recently BeMiller and co-workers[109] have synthesised *C*-(1→2)-disaccharides using a variation on this nitroaldol approach (Scheme 27). The electrophilic partner in this case is not an aldehyde but a nitroalkene (**80**) which undergoes a Michael-type reaction with the nucleophilic partner, the pyranosylnitromethane (**81**). The reaction produces a mixture of diastereoisomers (**82**). Treatment of one of these isomers with tributyltin hydride gave regioselective reduction to the oxime (**83**) which on deprotection gave the 2-*O*-β-D-mannopyranosyl-D-glucose mimic (**84**).

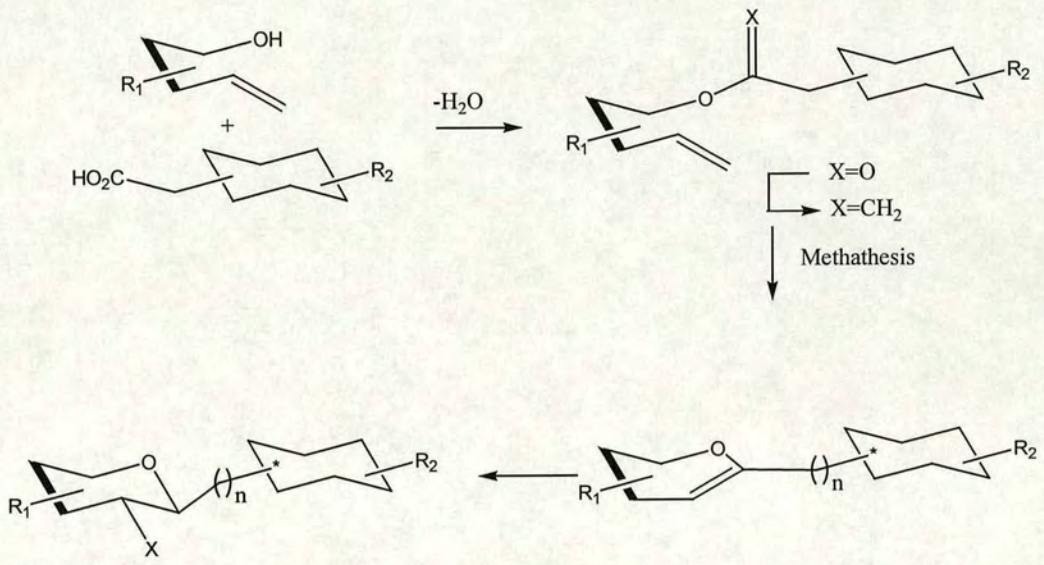


Scheme 27

1.6.7 Other approaches

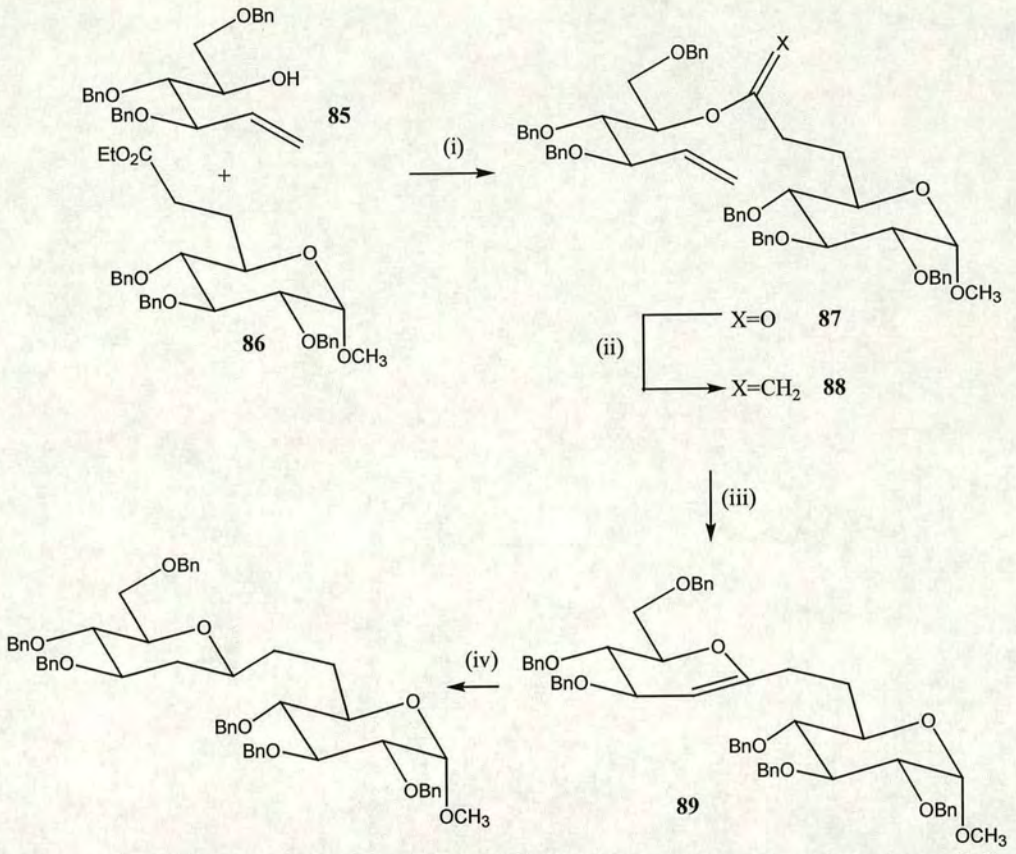
1.6.7.1 Metathesis

Postema and co-workers[110] have employed olefin metathesis as a route to *C*-glycosides and also *C*-disaccharides. The general principle behind the methodology is shown in Scheme 28.



Scheme 28

The first step involves coupling of an acid with an alcohol followed by methylenation of the ester carbonyl. Ring closing metathesis leads to the *C*-disaccharide glycal which can be manipulated to give the desired product. One of the examples reported by Postema involves coupling (**85**), derived from D-xylose and (**86**). Coupling of (**85**) and (**86**) using DCC lead to the ester (**87**) which was methylenated (**88**) using the method of Utimito *et al.*[111] Ring closing metathesis was achieved using Schrock's catalyst to give the glycal (**89**) which was hydroborated or hydrogenated using standard conditions (Scheme 29).

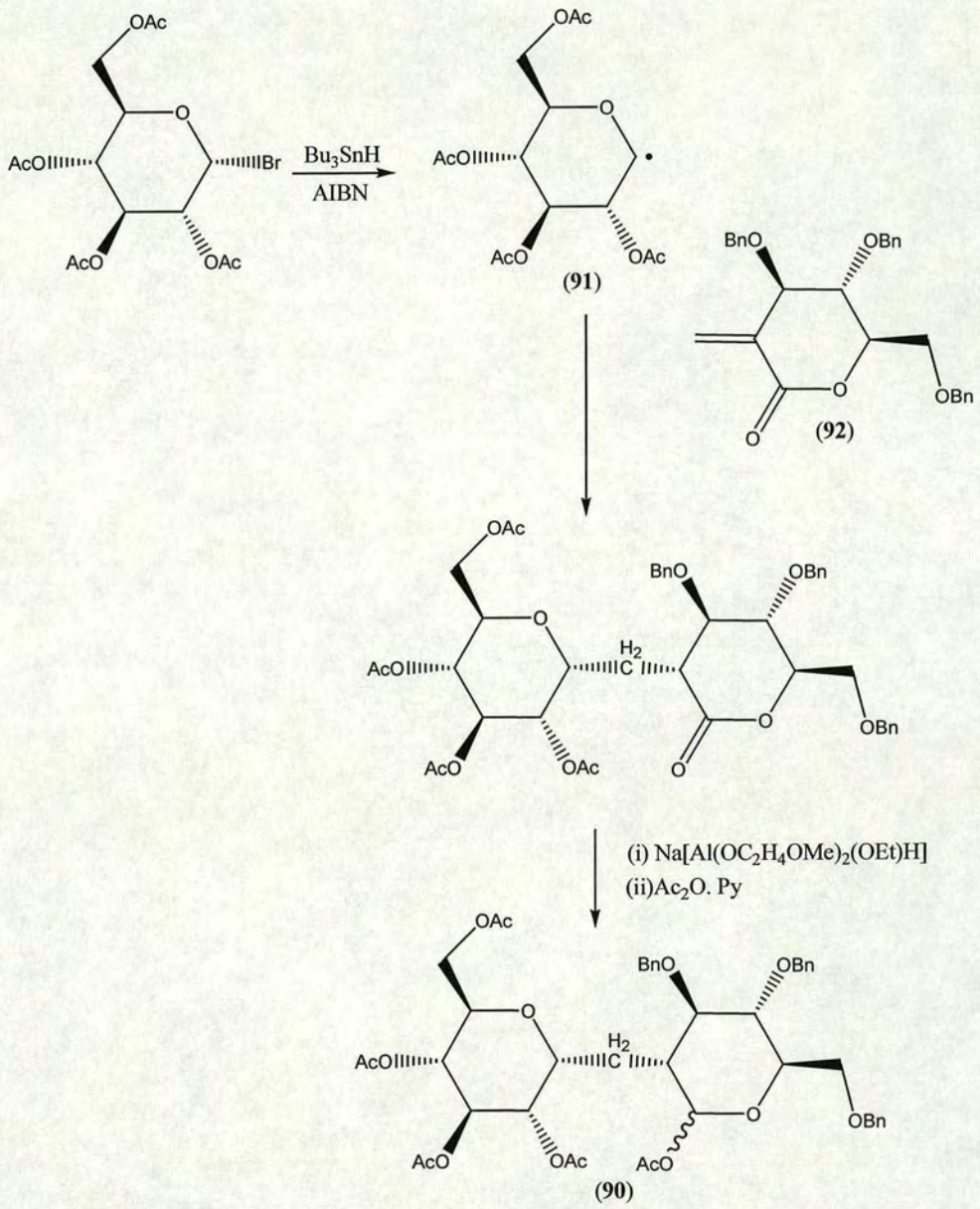


(i) DCC, 4-DMAP; (ii) $TiCl_4$, Zn Dust, $PbCl_2$, TMEDA, CH_2Br_2, (iii) Schrock catalyst, toluene, 60 C; (iv) H_2, Pd/C, Et_3N

Scheme 29

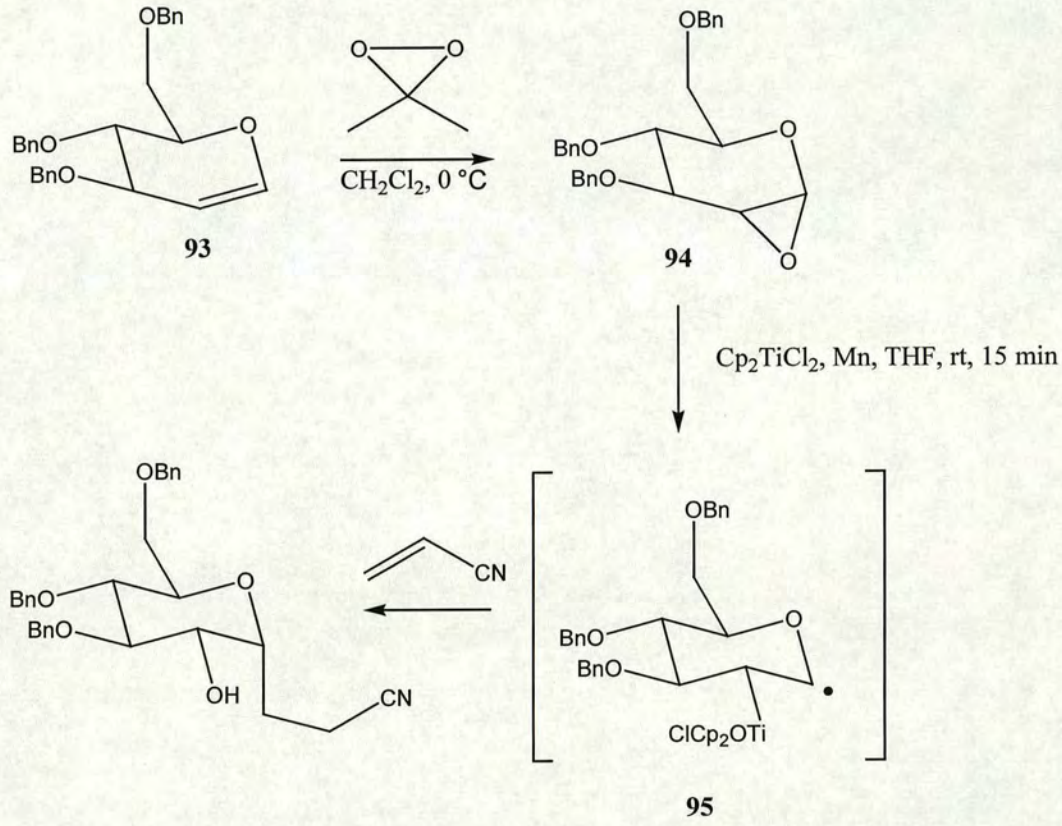
1.6.7.2 Radical addition

Free radical chemistry has found specific application in the formation of α-*C*-glycosides. Much of the original work was carried out by Giese and co-workers[112] and involved generation of anomeric radicals from glycosyl halides as highlighted by the synthesis of the *C*-disaccharide (**90**) (Scheme 30). The key steps were addition of the glycosyl derived radical (**91**) to the methylene lactone (**92**) followed by reduction to give the desired product (**90**).


OAc
AcO
Br
AcO
OAc
Bu_3SnH
AIBN
(91)
BnO
OBn
OBn
(92)
H_2C
(i) $Na[Al(OC_2H_4OMe)_2(OEt)H]$
(ii)Ac_2O. Py
(90)

Scheme 30

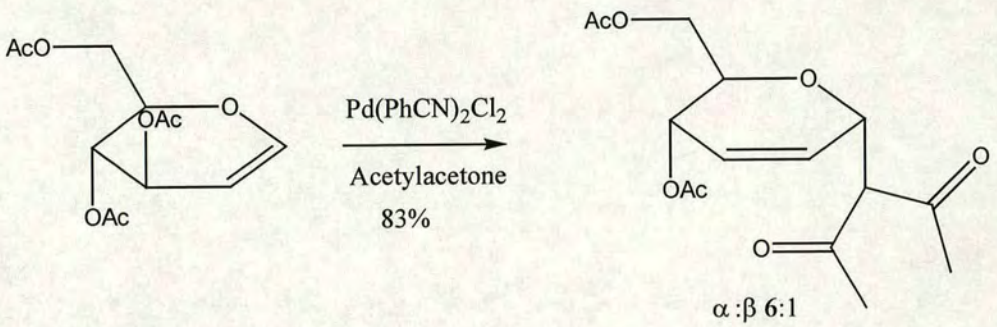
Recently, Little and Parrish[113] have reported a novel approach to anomeric radical formation involving titanocene-mediated cleavage of epoxides (Scheme 31). Treatment of tri-*O*-benzyl glucal (**93**) with dimethyldioxirane afforded the 1,2-anhydro sugar (**94**) which afforded the anomeric radical (**95**) by treatment with titanocene(III) chloride.



Scheme 31

1.6.7.3 Palladium mediated approaches to *C*-glycosides

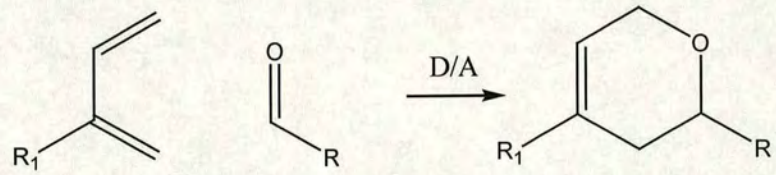
The synthetic utility of palladium chemistry has been adopted in *C*-glycoside synthesis. An example of work by Miwa and Yougai,[114] in which they examined the palladium catalysed reaction of dicarbonyl compounds with various glycals, is shown in Scheme 32.



Scheme 32

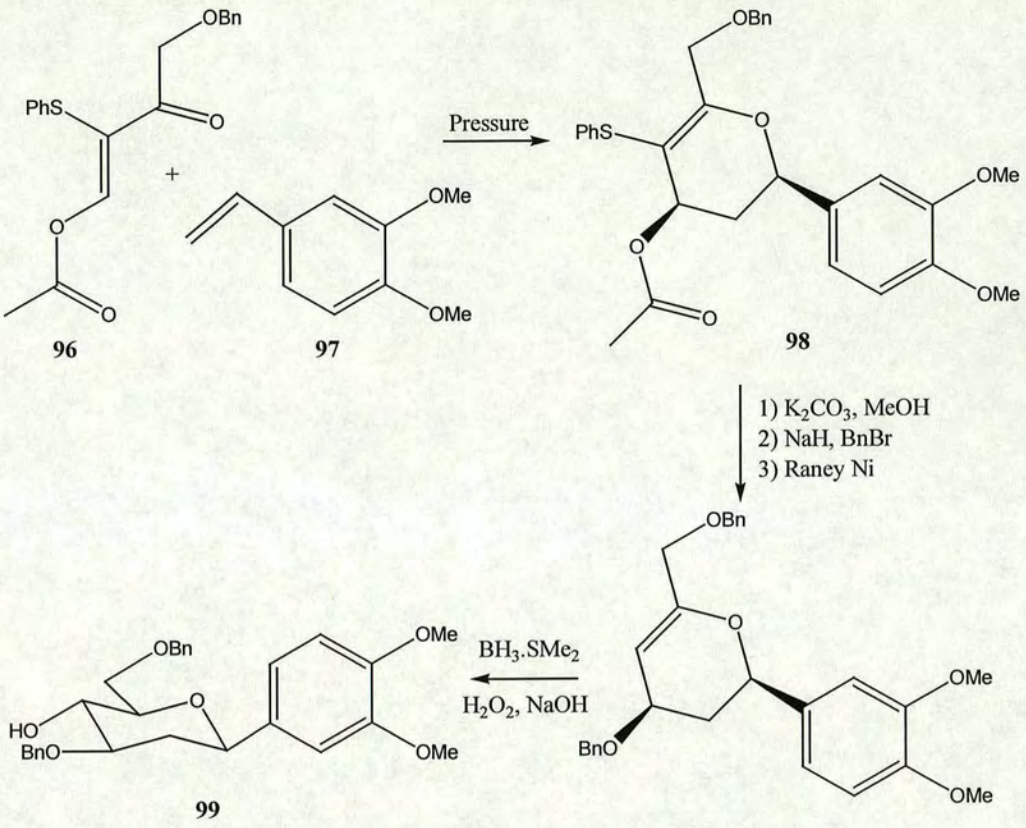
1.6.7.4 Cycloaddition reactions

The application of cycloaddition reactions to *C*-glycoside preparation is fairly recent. One such reaction is the hetero Diels-Alder cycloaddition where a carbonyl group acts as dienophile (Scheme 33)



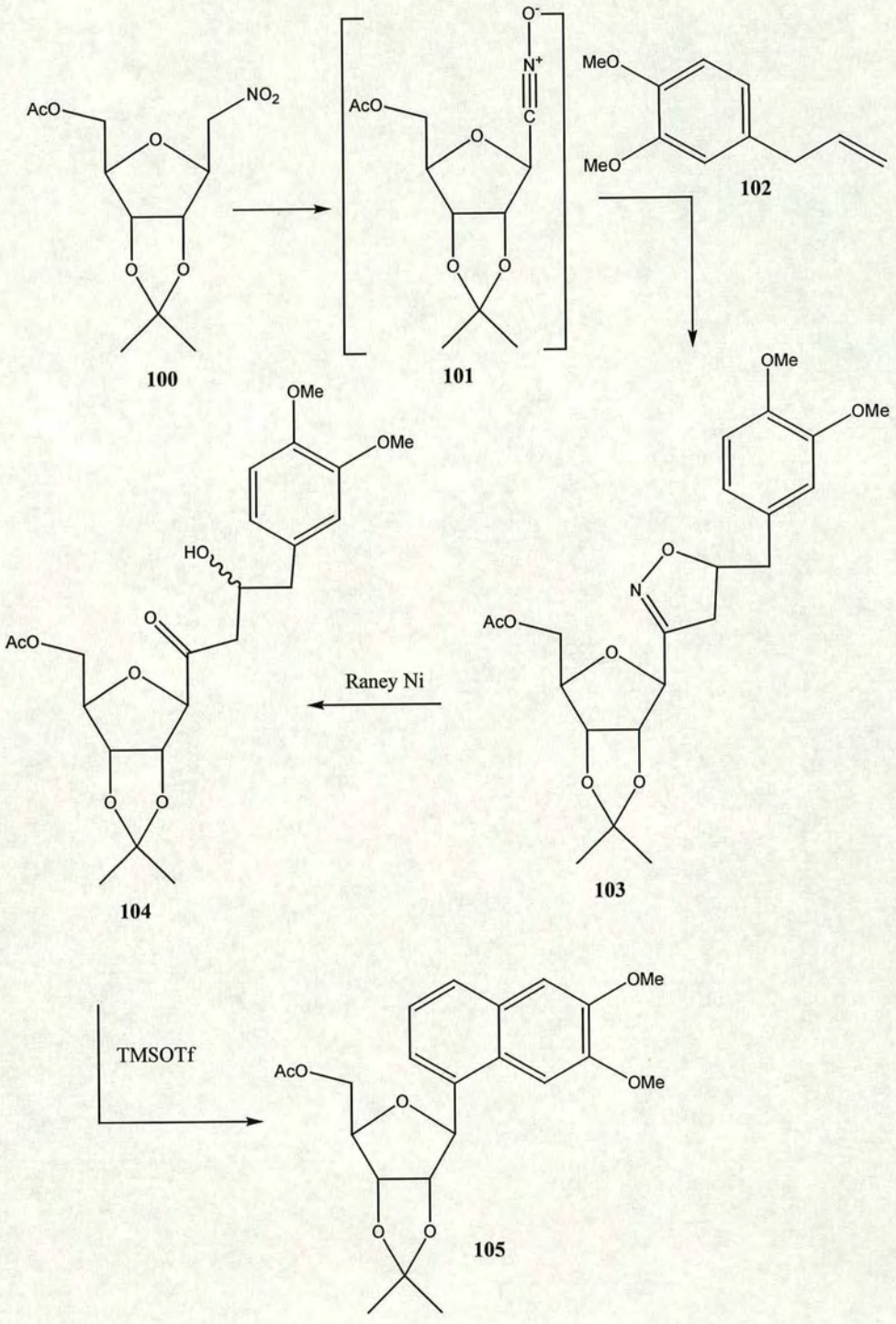
Scheme 33

Schmidt and co-workers[115] have utilised this methodology in the synthesis of aryl *C*-glycosides (Scheme 34). Under high pressure at 60°C the diene (**96**) and dienophile (**97**) underwent the hetero Diels-Alder cycloaddition to give adduct (**98**) which was deacteylated, benzylated and desulfurizated. Finally hydroboration followed by oxidative work up gave the desired aryl *C*-glycoside (**99**).



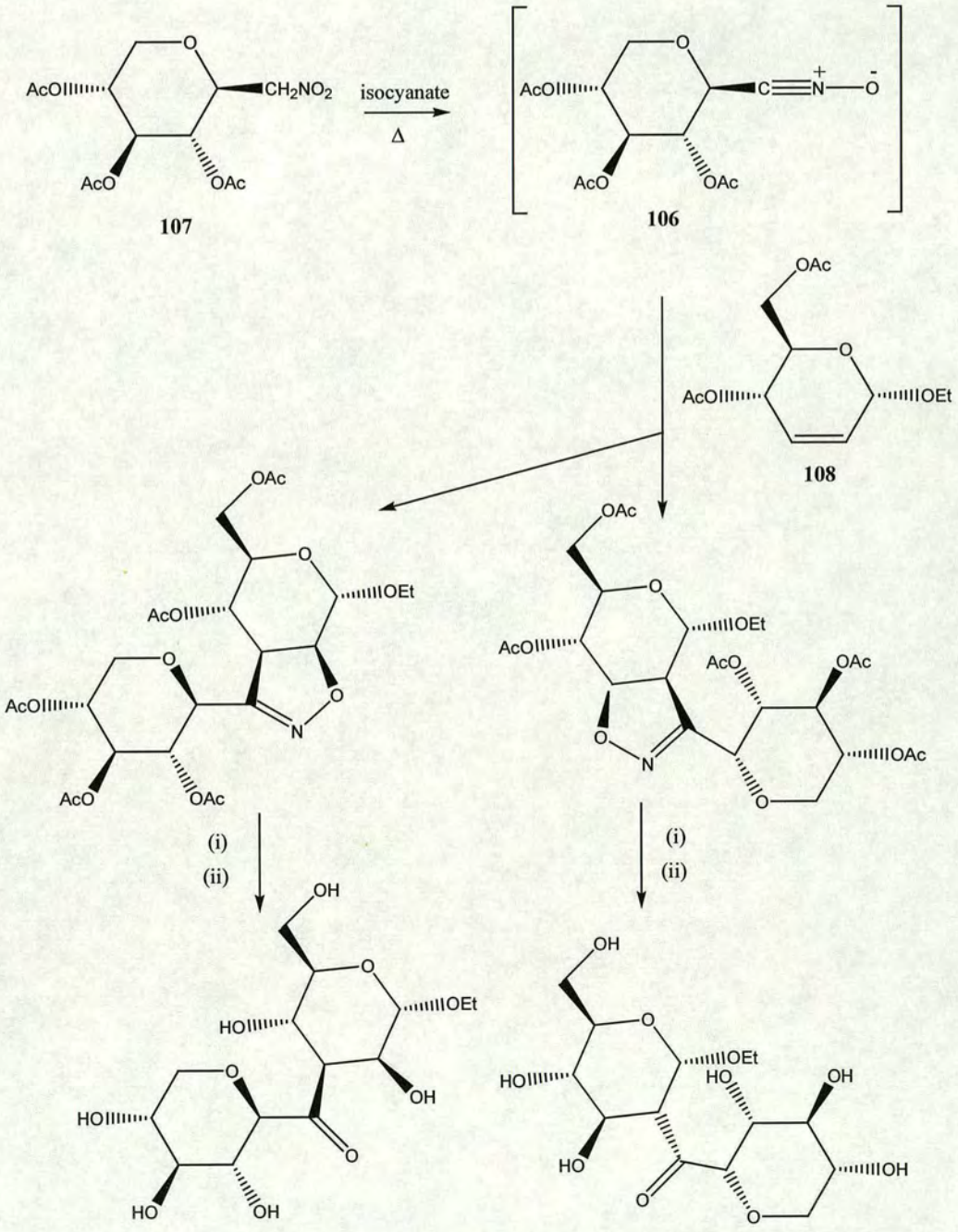
Scheme 34

Kozikowski *et al*[116] have used nitrile oxide chemistry in the synthesis of *C*-nucleoside analogues (Scheme 35). Starting from the furanosylnitromethane (**100**), the nitrile oxide (**101**) was generated by isocyanate-mediated dehydration and trapped with the alkene (**102**). Subsequent ring opening of the isoxazoline formed (**103**), and cyclisation and aromatisation of the resulting β-hydroxyketone (**104**), gave the target aryl *C*-glycoside (**105**).


AcO
NO2
O
O
O
100
O-
N+
C
AcO
O
O
O
101
MeO
MeO
102
OMe
OMe
HO
AcO
O
O
O
O
104
Raney Ni
OMe
OMe
O
N
AcO
O
O
O
103
TMSOTf
OMe
OMe
AcO
O
O
O
105

Scheme 35

This nitrile oxide / isoxazoline approach used by Kozikowski has also been adopted by Paton and co-workers[117] for the synthesis of (1→2) and (1→3) linked *C*-disaccharides (Scheme 36). The approach involves generation of pyranosyl nitrile oxides (**106**) by dehydration of the corresponding pyranosylnitromethane (**107**) and cycloaddition with a 2,3-unsaturated pyranose (**108**).

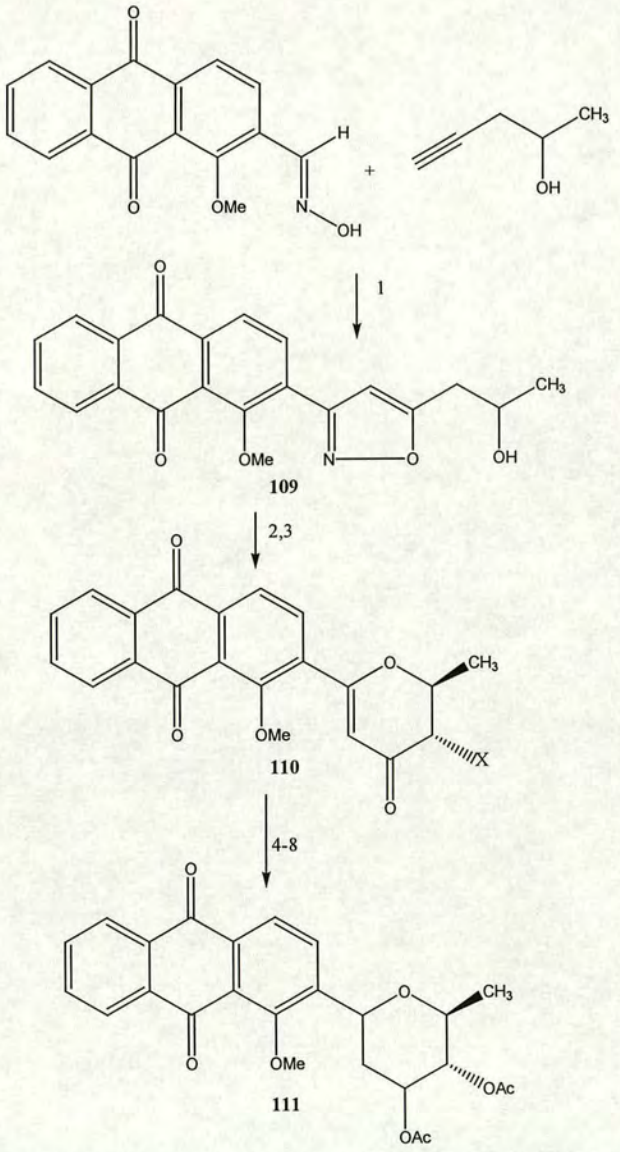


107 **106** **108**

i) KCN, MeOH; (ii) Raney Ni. H_2, $B(OH)_3$, MeOH, H_2O

Scheme 36

An alternative approach to *C*-glycosides using nitrile oxide / isoxazole chemistry has recently been reported by Hauser and Hu[118] (Scheme 37). In this route it is the sugar ring that is constructed *via* the cycloaddition reaction and subsequent manipulation. In the first step, the cycloaddition reaction gave the isoxazole (**109**), which was ring opened to the 1,3-diketone. This underwent an *in situ* cyclisation to give the arylpyranone (**110**). Treatment with $Mn(OAc)_4$ introduced the acetate group and hydrogenation under the conditions of Tius *et al*[119] gave reduction of the enone. Following reduction and acetylation the *C*-aryl glycoside was obtained (**111**).



1) NCS, CH_2Cl_2, 2) H_2, Ni(R), CH_3OH, H_2O, 3) HCl, THF, 4) $Mn(OAc)_3$, 5) H_2, Pd/C, K_2CO_3, DMSO, Heat, 6) $NaBH_3CN$, HCl, CH_3CH_2OH, 7) Ac_2O, Py, 8) CAN

Scheme 37

The successful application of cycloaddition chemistry to the synthesis of *C*-glycosides, as highlighted by the above examples, and previous work in the group, have prompted an investigation of nitrile oxide / isoxazoline chemistry as a route to *C*-glycosides. The findings are discussed in the following section.

2 Results and discussion

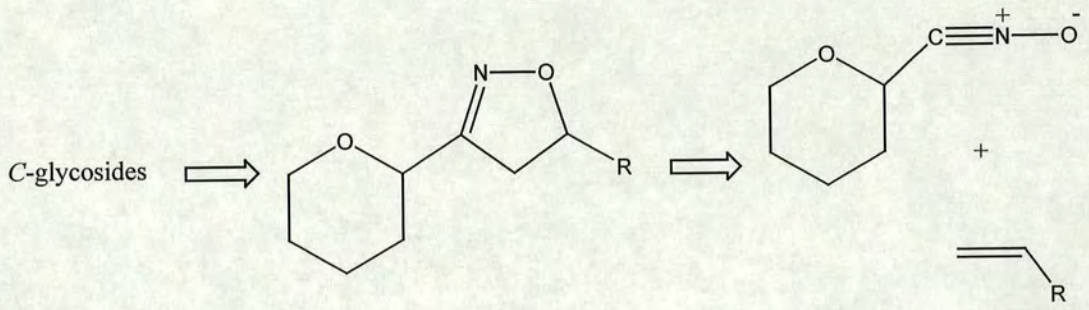
2.1 Programme of research

Recently, there has been renewed interest in the study of carbohydrate chemistry. This research is driven by discoveries such as the importance of cell surface carbohydrates in key molecular recognition events with protein receptors.[73] The hydrolytic instability of glycosides, however, makes their study much less straightforward and also reduces the likelihood of carbohydrate-based therapeutics due to their sensitivity to enzymatic cleavage and chemical hydrolysis. A possible solution to these problems is the use of *C*-glycosides, which are analogues of glycosides but with the exo-glycosidic oxygen replaced by carbon. These compounds may mimic glycosides but be resistant to degradation. One of the potential applications of *C*-glycosides is as glycosidase inhibitors. Inhibitors of this type have been shown to exhibit both antiviral[84] and antitumour activity[82] and have possible therapeutic application in the treatment of diabetes.[79] *C*-glycosides are also seen as chiral building blocks for macromolecules such as palytoxin[76] which contain *C*-disaccharide subunits, and interest in the synthesis of *C*-glycosides has been furthered by the discovery of naturally occurring *C*-nucleosides.

A number of synthetic approaches to *C*-glycosides have been developed indicating the wide range of chemistry applicable to carbohydrates. Most strategies are based on the natural electrophilic nature of the anomeric centre, but Wittig reactions,[103] palladium-mediated coupling,[114] radical addition reactions[117] and cycloaddition chemistry[116] have all been used (section 1.6). The successful application of cycloaddition chemistry has led to an investigation in this thesis of this approach to *C*-glycosides which should allow scope for the introduction of a wide variety of fuctionalisation.

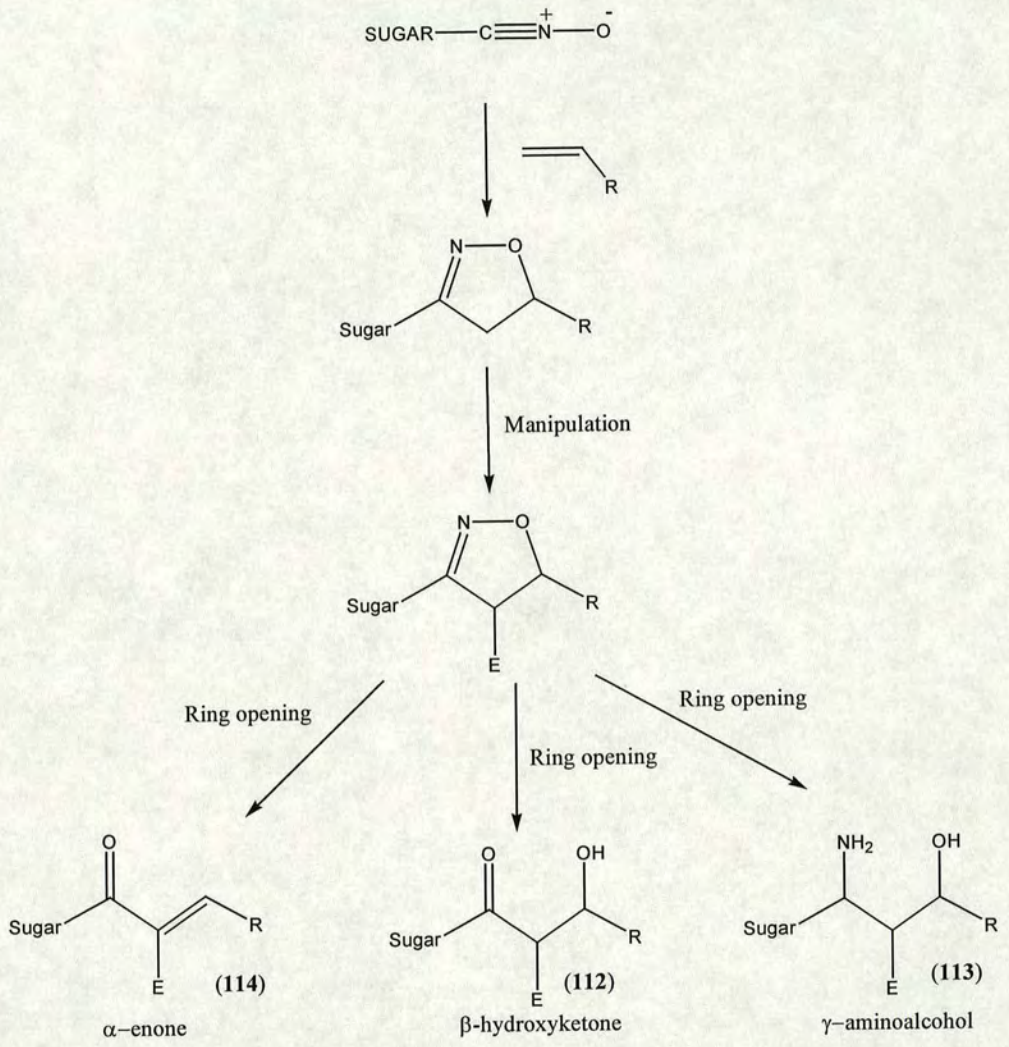
2.1.1 Synthetic strategy

Nitrile Oxide Cycloaddition chemistry (NOC) has been shown over the past few decades to be a valuable route to a variety of synthetic targets including natural products.[58] An attractive feature is the possibility of regio- and stereochemical control. The proposed route is shown in the retrosynthetic analysis (Scheme 38).



Scheme 38

The first step of the NOC route involves a [3+2] cycloaddition of the pyranosylnitrile oxide, with the functionality at the anomeric position, to a dipolarophile, usually an alkene (Scheme 39). The product of the cycloaddition is the key intermediate, the pyranosylisoxazoline, formed with predictable regio- and stereoselectivity. These 2-isoxazolines are sufficiently stable to allow modification of substituents, and substitution at the 4-position of the isoxazoline ring, thus increasing the range of functionality available. However, the main synthetic utility of the isoxazoline is the ability to cleave the N-O bond to release either the β-hydroxyketone (**112**), γ-aminoalcohol (**113**) or α-enone (**114**), depending on the conditions used. Thus a wide range of *C*-glycosides should be accessible. The NOC methodology has already been used in the synthesis of higher monoaccharides,[120] iminosugars[63] and 1,3-linked *C*-disaccharides.[117]

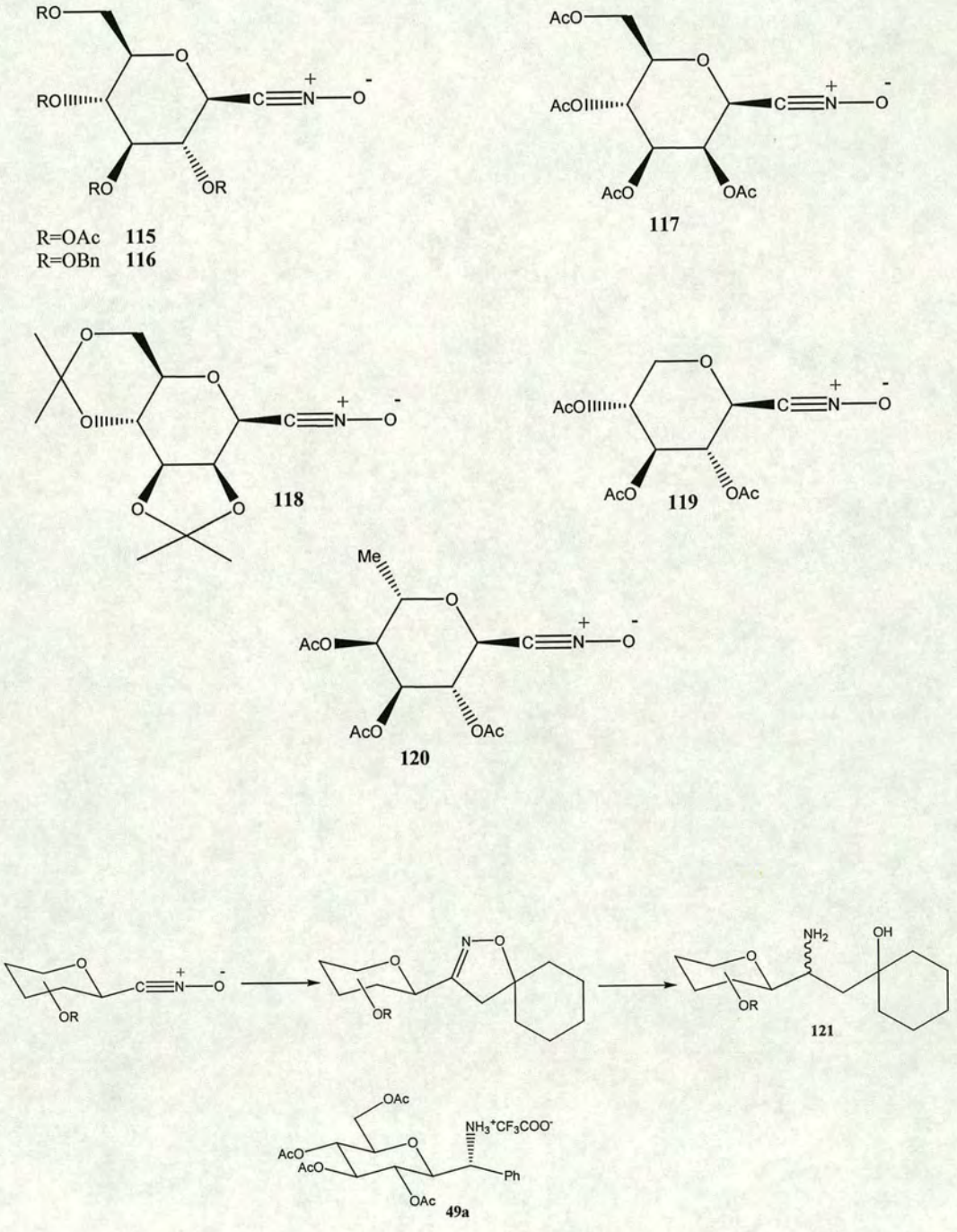


Scheme 39

The prime objective of the work described in this thesis was to investigate routes to pyranosylnitrile oxides and their subsequent cycloaddition reactions. Other goals included study of possible manipulation reactions and optimisation of the conditions required for ring opening of the carbohydrate isoxazolines.

The pyranosylnitrile oxides chosen for study were derived from D-glucose (**115, 116**), D-mannose (**117, 118**), D-xylose (**119**) and L-fucose (**120**). These were generated either directly or indirectly from the corresponding 2,6-anhydro-1-deoxy-1-nitroalditols. The

dipolarophiles were mainly commercially available achiral alkenes. Model reactions were carried out using methylenecyclohexane as the isoxazoline formed would be a single isomer. This dipolarophile could also be used in the synthesis of *C*-glycosides similar to the glycosidase inhibitor reported by Schmidt[77] as shown in Scheme 40.



Scheme 40

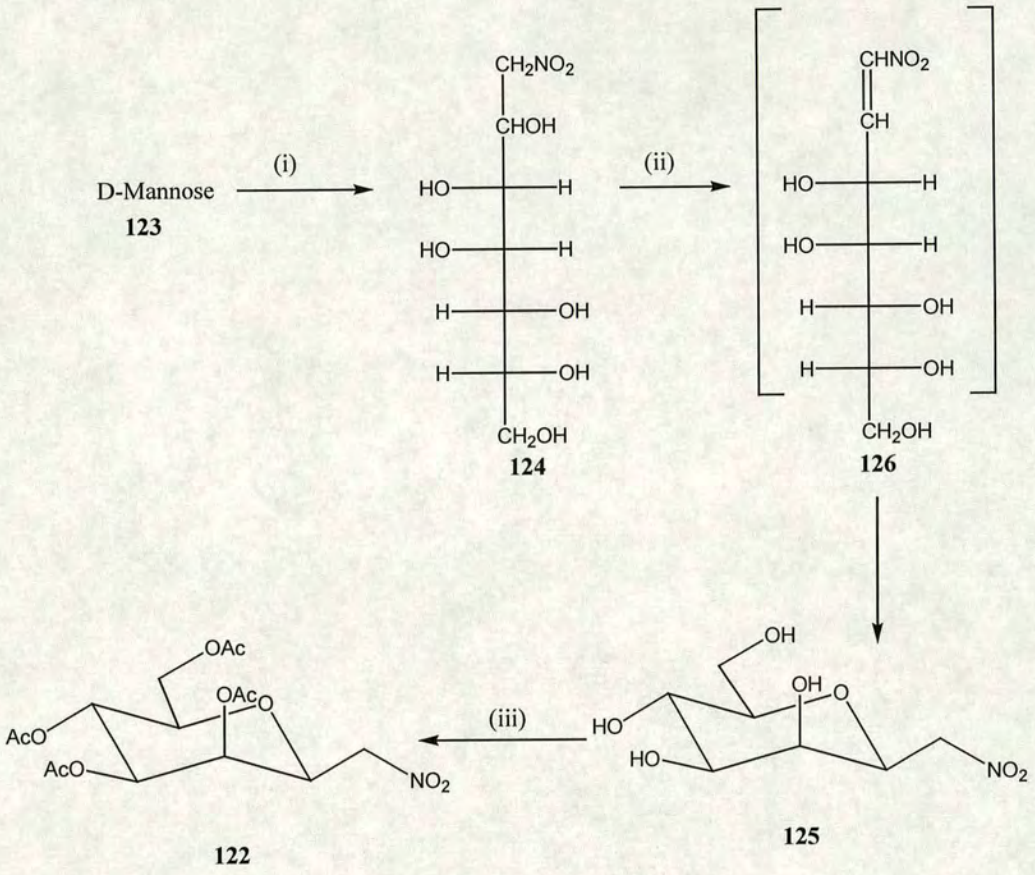
2.2 Synthesis of nitrile oxide precursors

The first step of the NOC route involves cycloaddition of pyranosylnitrile oxides, thus precursors to these nitrile oxides were required. The existing route to pyranosylnitrile oxides had involved Mukaiyama-type[9] dehydration of pyranosylnitromethanes, so the synthesis of a number of these compounds was undertaken. Of those chosen, the D-glucose, D-mannose and D-xylose-derived nitromethyl sugars were selected due to the commercial availability of the starting materials, the parent monosaccharides, and the common nature of these monosaccharides in biological systems. L-Fucose was chosen as it is an important component in partial structures of bacterial polysaccharides[121] and glycoproteins.[122]

Previous work within the group,[123,124,125] had shown that acetylated pyranosylnitromethanes provide access to pyranosylnitrile oxides and that an acetate-protection strategy had been widely successful. Thus, per-acetylated 2,6-anhydro-1-deoxy-nitroalditols were prepared from the corresponding aldoses using a modified version of the procedure of Köll *et al*[106] as outlined for the mannose-derived compound (**122**) in Scheme 41.

2.2.1 Synthesis of acetylated 2,6-anhydro-1-deoxy-nitroalditols

Tetra-O-acetyl-β-D-mannopyranosylnitromethane (**122**) was synthesised in three steps from D-mannose (**123**) as outlined in Scheme 41. In the first stage, base catalysed addition of nitromethane to D-mannose in its acyclic form gave the nitroalditol (**124**) as described by Fischer and Sowden.[126] The product was not isolated but converted directly to the β-mannopyranosylnitromethane (**125**) by heating in water. The mechanism is believed to involve dehydration to the α-nitro olefin (**126**) followed by thermal cyclisation. Acid catalysed acetylation yielded the title compound (**122**) (31%).



(i) CH_3NO_2, NaOMe, MeOH; (ii) H_2O, reflux, (iii) Ac_2O, CF_3SO_3H

Scheme 41

There are two possible chair conformations for each of the α- and β-anomers. Of the four possible chair arrangements (Figure 6) the β-isomer in the $^5C_2$ conformation is the structure with the least number of substituents in the axial position. The β-anomer would be predicted to be formed preferentially over the α-anomer during the cyclisation step, as in the α-isomer the nitromethyl group or the C-6 substituent is in the axial position.

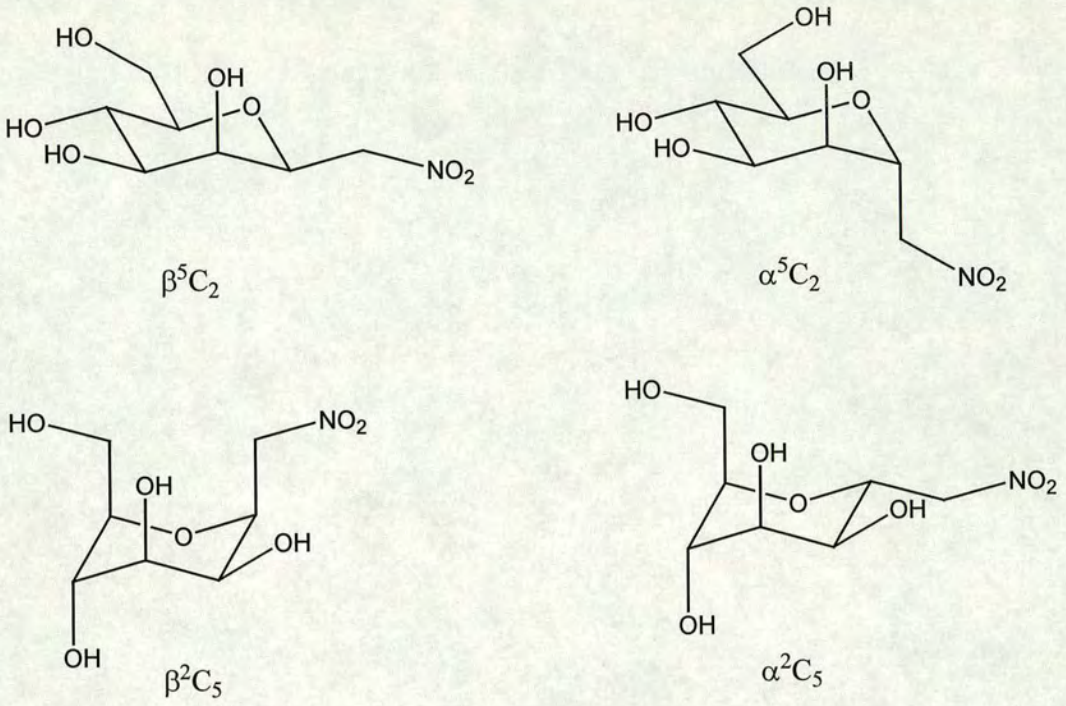
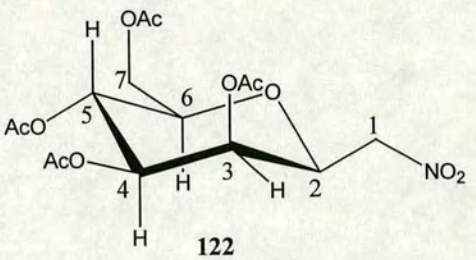


Figure 6

The predicted $^5C_2$ conformation is supported by the ^{1}H NMR coupling constant data. Table 1 shows the ^3J couplings for the ring protons of the acetylated mannopyranosylnitromethane (**122**). The $J_{2\text{-}3}$ coupling of 0.8 Hz is indicative of the equatorial-axial coupling seen for the β-anomer, as is the $J_{3\text{-}4}$ of 3.4 Hz. The value of 10.0 Hz for the $J_{4\text{-}5}$ and $J_{5\text{-}6}$ couplings are in agreement with the two di-axial couplings. Sowden[127] has shown that the β:α ratio during the cyclisation is in the order of 50:1.

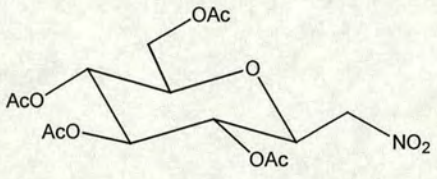
Coupling	*J*/Hz
2,3	0.8
3,4	3.4
4,5	10.0
5,6	10.0



122

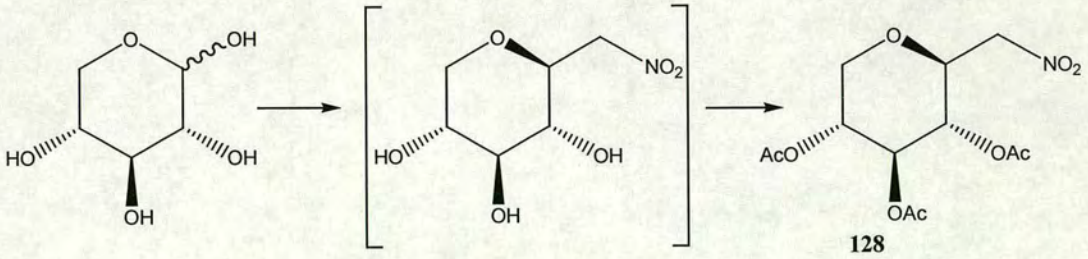
Table 1: Coupling constants for (**122**)

The peracetylated glucose-derived nitromethyl compound (**127**) was prepared in similar fashion from D-glucose in a 25 % overall yield.



127

2.2.2 Synthesis of tri-*O*-acetyl-β-D-xylopyranosylnitromethane (128) **and tri-*O*-acetyl-β-L-fucopyranosylnitromethane** (129)**.**



128

Scheme 42

The relatively low yields for the formation of the nitromethyl compounds (**122**) and (**127**) were disappointing, thus the experimental procedure was modified. The first change made was to not isolate the 2,6-anhydro-1-deoxy-nitroalditol, but to acetylate the crude reaction mixture and obtain the product directly (Scheme 42). This worked well for both tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**128**) (68%) and tri-*O*-acetyl-β-L-fucoypyranosylnitromethane (**129**) (70%) with recrystallisation giving the products without the need for further purification. An added advantage of this method is the removal for the need to carry out liquid/liquid extraction required to isolate the unprotected 2,6-anhydro-1-deoxy-nitroalditol. This is a time consuming process requiring the use of large amounts of solvent.

For both (**128**) and (**129**) no α-isomer was isolated. This observation can be explained using the same reasoning as for tetra-*O*-acetyl-β-D-mannopyranosylnitromethane (**122**). For tri-*O*-acetyl-β-L-fucopyranosylnitromethane (**129**) the least hindered arrangement is the $^{2}C_{5}$ conformation of the β-isomer. A $J_{2,3}$ coupling constant of 9.2 Hz confirms the diaxial geometry supporting the assignment of the β-configuration. The large coupling constant, 9.8 Hz, for $J_{3,4}$ is as expected for the diaxial arrangement, whilst the small 2.7 Hz coupling for the 4-5 protons is consistent with the equatorial – axial relationship.

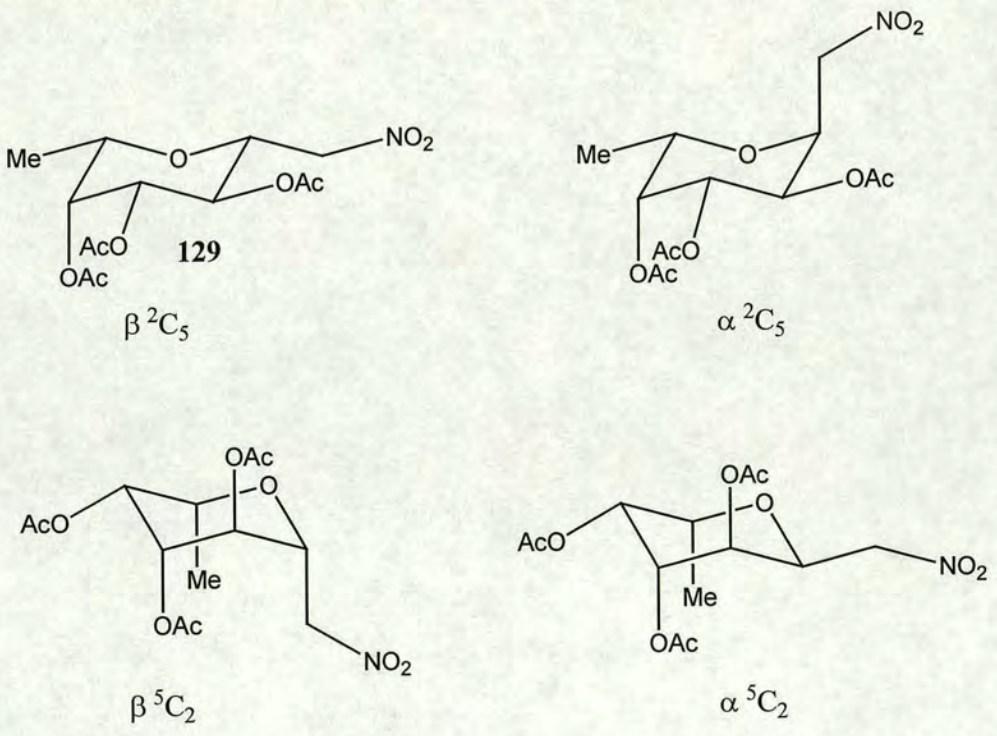
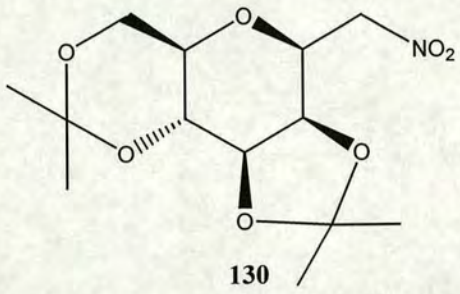


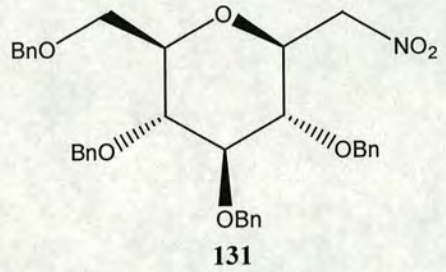
Figure 7

2.2.3 Alternative protection strategies

To increase the scope of possible reactions of pyranosylnitrile oxides and their derivatives, it was decided to investigate alternative protection strategies. Study of the literature showed two possible base-stable alternatives: actetals and benzyl ethers in the form of 3,4:5,7-di-*O*-isopropylidene-β-*D*-mannopyranosylnitromethane (**130**)[128] and 3,4,5,7-tetra-*O*-benzyl-β-D-glucosylnitromethane (**131**).[129]



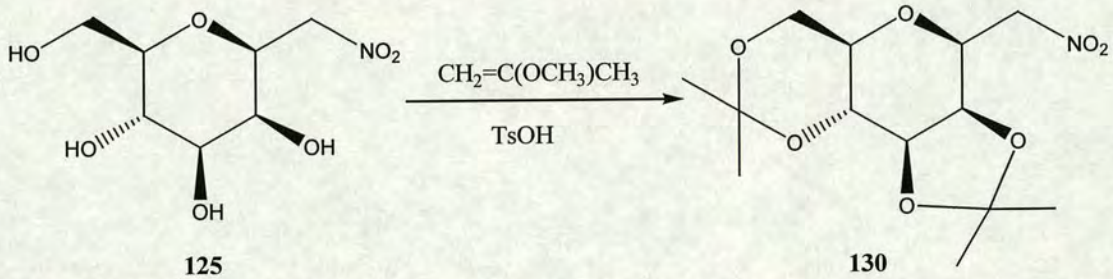
130



131

2.2.3.1 Synthesis of 3,4:5,7-di-*O*-isopropylidene-β-*D*-mannopyranosylnitromethane (130)

Acetonation of pyranosylnitromethanes was first reported by BeMiller *et al.*[128] They describe the synthesis of various di-*O*-isopropylidene protected nitromethylsugars. For example (**130**) was synthesised from β-*D*-mannopyranosylnitromethane (**125**) (Scheme 43).



125 **130**

Scheme 43

Initial attempts at acetonation with β-*D*-mannopyranosylnitromethane (**125**) using the conditions reported by BeMiller *et al* afforded the desired product (**130**), but in consistently low yield (<50%) with column chromatography required to isolate the product. However, modification of the reported experimental procedure allowed kinetically controlled acetonation *via* treatment of the parent β-*D*-mannopyranosylnitromethane (**125**) with an

excess of 2-methoxypropene and a catalytic amount of 4-toluenesulfonic acid (Scheme 43). The product (**130**) was isolated by recrystallisation as a white solid in 81% yield and characterised using ^{1}H and ^{13}C NMR spectroscopy.

Fusion of the dioxolane at C(2)-C(3) causes distortion of the pyranose ring from the usual chair conformation. This is evident by comparing the coupling constants in the ^{1}H NMR spectra for 3,4:5,7-di-*O*-isopropylidene-β-*D*-mannopyranosylnitromethane (**130**) and 3,4,5,7-tetra-*O*-acetyl-β-*D*-mannopyranosylnitromethane (**122**) (Table 2). These show significant variation in some of the coupling constants caused by a slight flattening of the pyranose ring due to constraints caused by the fused 1,3-dioxane and 1,3-dioxalane rings. Thus, the structure deviates from the ideal $^{5}C_{2}$ arrangement. The couplings between the 2-3 and 3-4 protons show the greatest deviation due to these being the site of ring fusion. The spectrum also contains peaks at 1.31, 1.39, 1.47, and 1.51 ppm corresponding to the expected four CH_3 groups of the isopropylidene protection. The ^{3}J values, shown in Table 2, are in agreement with the predicted structure; the β-isomer with a distorted $^{5}C_{2}$ conformation. Two small couplings are seen for $J_{2,3}$ and $J_{3,4}$ (2.5 and 5.4 Hz), whilst two large couplings are seen for $J_{4\text{-}5}$ and $J_{5\text{-}6}$ (7.9 and 10.0 Hz) due to two diaxial couplings. The ^{13}C spectrum contains peaks at 18.6, 26.2, 28.1 and 28.8 ppm corresponding to the four CH_3 groups and quaternary peaks at 99.6 ppm and 110.3 ppm corresponding to the 6-membered 1,3-dioxane ring and 5-membered 1,3-dioxolane ring respectively.

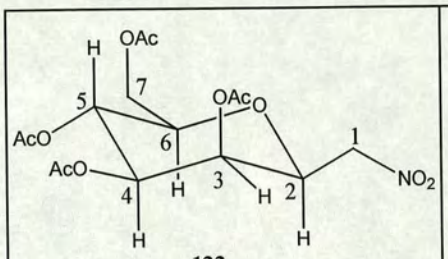
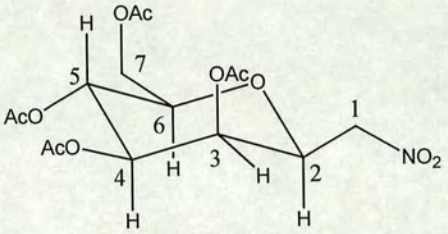
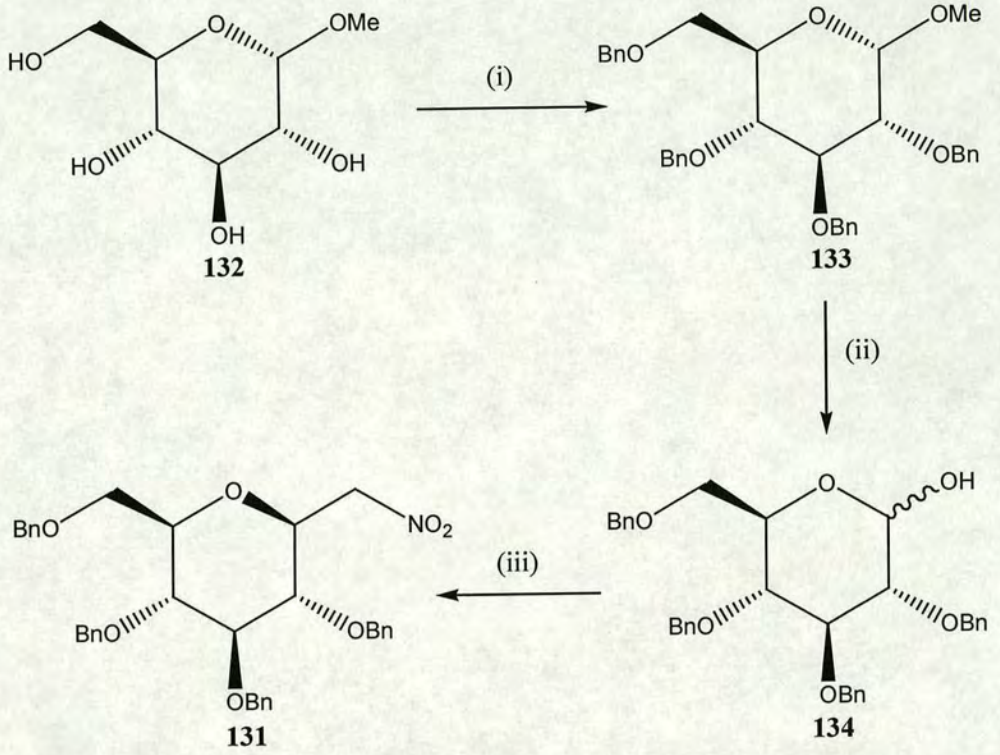
 **122**		 **122**	
	J / Hz		*J* / Hz
$J_{1\text{-}1'}$	13.0	$J_{1\text{-}1'}$	14.1
$J_{1\text{-}2}$	9.8	$J_{1\text{-}2}$	9.9
$J_{1'\text{-}2}$	1.2	$J_{1'\text{-}2}$	2.9
$J_{2\text{-}3}$	0.7	$J_{2\text{-}3}$	2.5
$J_{3\text{-}4}$	3.4	$J_{3\text{-}4}$	5.4
$J_{4\text{-}5}$	10.0	$J_{4\text{-}5}$	7.9
$J_{5\text{-}6}$	10.0	$J_{5\text{-}6}$	10.1
$J_{6\text{-}7}$	2.3	$J_{6\text{-}7}$	5.7
$J_{6\text{-}7'}$	5.7	$J_{6\text{-}7'}$	10.1
$J_{7\text{-}7'}$	12.4	$J_{7\text{-}7'}$	10.9

Table 2: Comparison of coupling constants between (**122**) and (**130**)

2.2.3.2 Synthesis of 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (131)

This compound was synthesised in three steps from α-methyl glucoside (**132**) as outlined in Scheme 44. The first step involved protection of the free hydroxyl groups as benzyl ethers followed by hydrolysis of the anomeric acetal and finally base-catalysed reaction with nitromethane.



(i) NaH, BnBr, (ii) Glacial Acetic acid, 2M H_2SO_4, (iii) CH_3NO_2, 1,2-diaminoethane

Scheme 44

Treatment of methyl α-D-glucopyranoside (**132**) with sodium hydride and benzyl bromide gave an oil that was purified by column chromatography to afford methyl 2,3:4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**133**) in 52% yield. Excess benzyl bromide was removed from the reaction mixture by addition of triethylamine. The benzyl triethylammonium bromide formed was removed by an aqueous wash. The couplings in the ^{1}H NMR were in agreement with the predicted structure with a $J_{1,2}$ value of 3.6 Hz consistent with the equatorial-axial arrangement of the α-anomer.

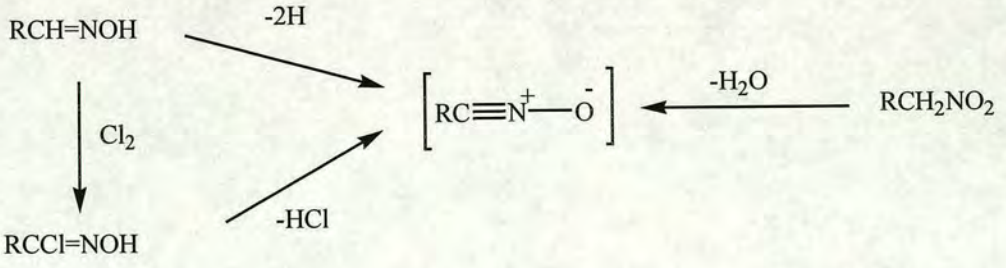
Hydrolysis of the acetal was achieved by heating (**133**) at 90 °C for 18 hrs in the presence of 2M H_2SO_4 and glacial acetic acid. The product (**134**) was obtained as a white crystalline solid in 33% yield and ^{1}H NMR spectroscopy showed that a mixture of anomers had been obtained.

The target compound (**131**) was synthesised from (**134**) using the procedure of Stick *et al*[129] involving treatment with 1,2-diaminoethane and nitromethane with heating to 80°C for 14 days. The product, 2,3:4,6-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (**131**), was isolated by dry flash chromatography as a clear oil (72%) that solidified on standing. Only the β-isomer of the product was obtained, this being confirmed by the $J_{2,3}$ coupling of 9.8 Hz.

2.3 Alternative sources of pyranosylnitrile oxides

As mentioned before, the previous route to pyranosylnitrile oxides involved isocyanate-induced dehydration of nitromethyl sugars using a modification of the Mukaiyama method.[9] This, in general, has proved to be an excellent approach as the pyranosylnitrile oxides are generated in good yields from cheap readily available starting materials. However, there are a number of features of the reaction which make it incompatible with certain dipolarophiles. For instance, the reaction requires prolonged reaction times at elevated temperatures. Thus, low boiling or thermally unstable dipolarophiles, e.g. DMAD which polymerises at high temperatures, are not compatible with the route. Also, the isocyanate used as dehydrating agent can undergo side reactions with certain functional groups found in the dipolarophiles; for example it would react with alcohols to afford urethanes. To avoid these problems, attempts were made to find alternative sources.

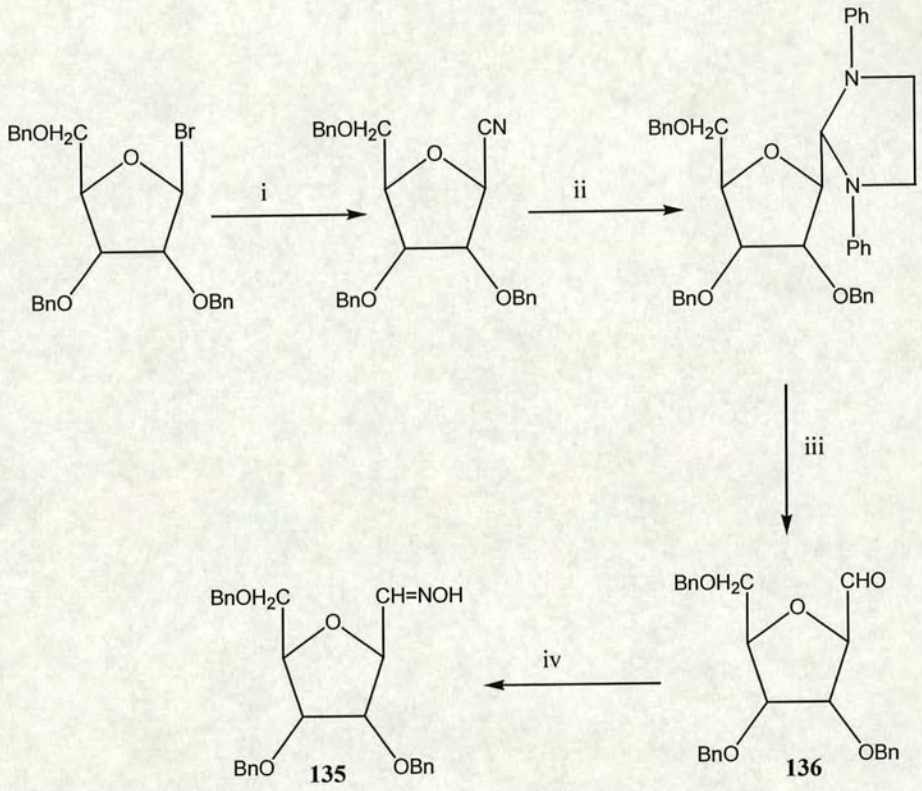
The most common literature routes to nitrile oxides are shown in Scheme 45. They involve the aforementioned isocyanate-induced dehydration of nitromethylcompounds, oxidation of aldoximes and dehydrochlorination of hydroximoyl chlorides. It was therefore decided to attempt to synthesise pyranosylaldoximes and hydroximoyl chlorides.



Scheme 45

2.3.1 Synthesis of pyranosylaldoximes

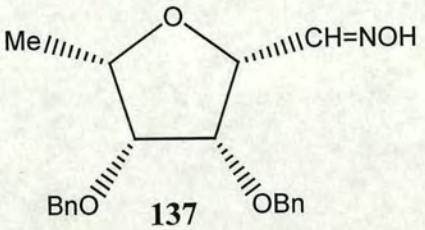
A search of the literature showed that the only examples of sugar-derived aldoximes with the oximic group at the anomeric position were *C*-furanosyl aldoximes (**135**). The first example was reported by Moffat *et al*[130] in 1973. This route involved a three step synthesis of the formyl *C*-furanoside (**136**) followed by oximation (Scheme 46).



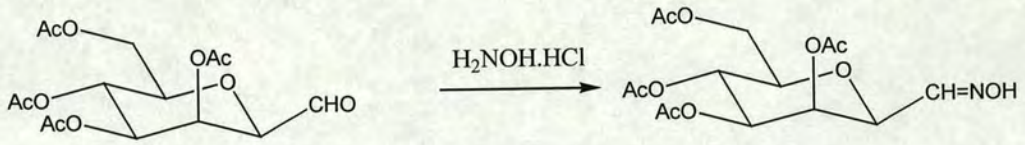
i) $Hg(CN)_2$, ii) Raney Nickel, $PhNH(CH_2)_2NHPH$ NaH_2PO_2, HOAc-Py-H_2O, iii) p-TsOH, AcOH, iv) $H_2NOH.HCl$, EtOH, Pyridine

Scheme 46

A similar approach has been reported by Popsavin *et al*[131] which also involves conversion of the formyl *C*-furanoside (**136**) to the oxime. Vassella *et al*[132] have published the synthesis of (**137**) as a by-product in the synthesis of a cyclic nitrone.

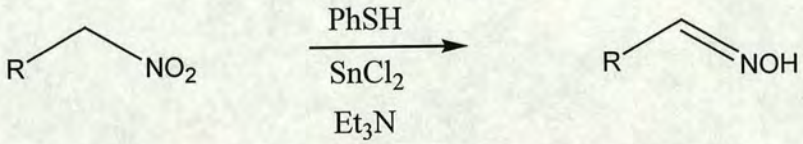


Oximation of formyl *C*-glycosides was considered as a route to pyranosylaldoximes (Scheme 47).There are a number of routes in the literature to formyl *C*-glycosides including work by Dondoni and co-workers[101] (see section 1.6.4). However, none of the syntheses are straightforward often requiring multiple steps, expensive reagents and/or forcing conditions. Also, once prepared the aldehyde is prone to oxidation and hydration as well as elimination. These problems prompted a search for alternative approaches.



Scheme 47

The method selected was based on the observation by Bartra *et al*[133] that primary aliphatic nitro compounds can be reduced to aldoximes by stannate(II) complexes generated from $SnCl_2$ (Scheme 48). The reaction is reported to be suitable for a wide range of aliphatic and aromatic nitro-compounds and offers excellent yields and rapid reaction times under mild conditions. Therefore, it was considered to be a good candidate for use with the pyranosylnitromethyl sugars. A major attraction of this route was that the oxime would be synthesised from the previously prepared pyranosylnitromethyl compound.

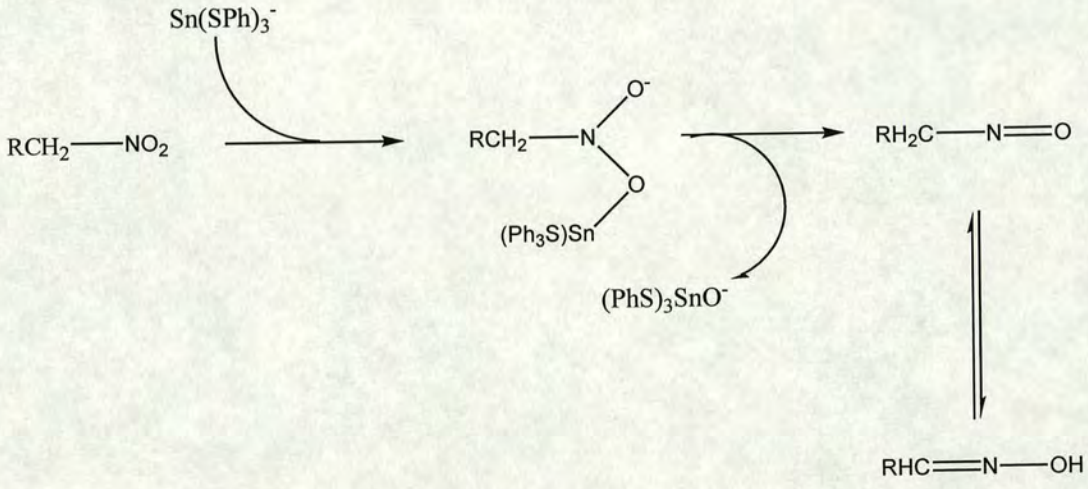


Scheme 48

The aforementioned stannate(II) complex, $[Et_3NH][Sn(SPh)_3]$ is generated *in situ* from tin(II) chloride, thiophenol and triethylamine. Attempts to isolate this species by Bartra *et al*[133] led to $Sn(SPh)_2$ precipitation, indicating a rapid equilibrium between the reagents and the tin complex (Scheme 49).

Scheme 49

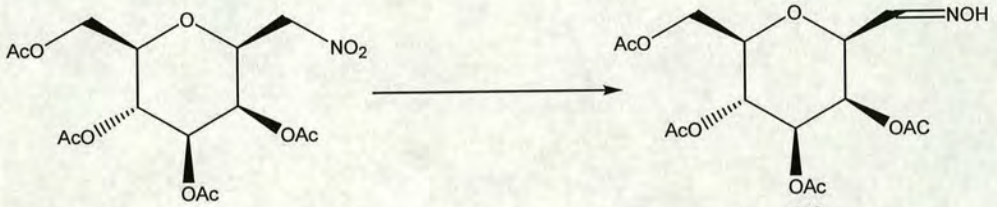
The proposed mechanism is outlined in Scheme 50. The fact that the oxime is not further reduced, along with Bartra's[133] observation that nitrosobenzene is reduced even more rapidly than nitrobenzene under the reaction conditions, support the proposed mechanism. Reduction to the corresponding hydroxylamine is only seen for secondary nitroalkanes in apolar solvents. For primary nitro-compounds further reduction is prevented by rapid nitroso to oxime tautomerism.



Scheme 50

The method of Bartra[133] was tested on tetra-O-acetyl-β-D-mannopyranosylnitromethane (**122**) with treatment with tin(II) chloride, triethylamine and thiophenol affording the D-mannose derived aldoxime (**138**) (Scheme 51). The product was separated from tin-based by-products and other impurities by chromatography and isolated in 84% yield as a mixture of E:Z isomers in a 70:30 ratio. The ^{1}H NMR spectrum of the products shows a doublet for each of the isomers due to the 1-H proton at 7.30 ppm (E-isomer) and 6.69 ppm (Z) isomer. The assignment of geometry was made by comparison with literature values,[134] and the isomer ratio determined from the integrals of these signals. There are also characteristic OH signals in the ^{1}H NMR at 8.53 ppm (E-isomer) and 7.79 ppm (Z-isomer) corresponding to

the NOH of each isomer. The couplings of the sugar ring protons are similar to those of the parent nitromethyl compound. The ^{13}C NMR spectra shows a diagnostic peak at 146.1 ppm (E-isomer) and 147.2 ppm (Z-isomer) corresponding to the CH=NOH.



Scheme 51

The structure of (**138**), and the β-configuration at the anomeric centre in particular, was confirmed by X-ray crystallography (Figure 8). A noteworthy feature of the crystal structure is the disorder in the region of the oxime moiety. There are two distinct arrangements represented by O(1)-N(1)-C(1)-C(2) and O(1')-N(1')-C(1)-C(2), corresponding to the *Z*- and *E*-oxime configurations. Thus both isomers detected in solution by NMR spectroscopy are incorporated within the crystal lattice. The ratio in the crystal, however, is 75 *Z* : 25 *E*, whereas the *E*-isomer predominates in solution.

The structure of the sugar ring is as expected for a β-D-mannopyranosyl compound. The Cremer and Pople puckering parameters[135] [Q = 0.580 Å, θ = 3.5°, ϕ = 228.7°] for the six-membered ring comprising C(2)-C(3)-C(4)-C(5)-C(6)-O(6) show that it adopts a predominantly $^5C_2$ conformation. In particular, the θ value of 3.5° is close to the theoretical value for the chair conformation (θ = 0°). This arrangement is reflected in the ^1H NMR couplings involving the ring hydrogens [$J_{2,3}$ 1.1, $J_{3,4}$ 3.3, $J_{4,5}$ 10.1, $J_{5,6}$ 10.0 Hz]. For the oxime moiety, the observed ^1H NMR couplings of 5.5 and 4.1 Hz between 1-H of the oxime and 2-H of the pyranose ring are also consistent with the torsion angles in the crystal of 129.8° and 144.8° for H(1)-C(1)-C(2)-H(2) and H(1')-C(1)-C(2)-H(2), suggesting that for both isomers the conformation in solution is broadly similar to that in the crystal.

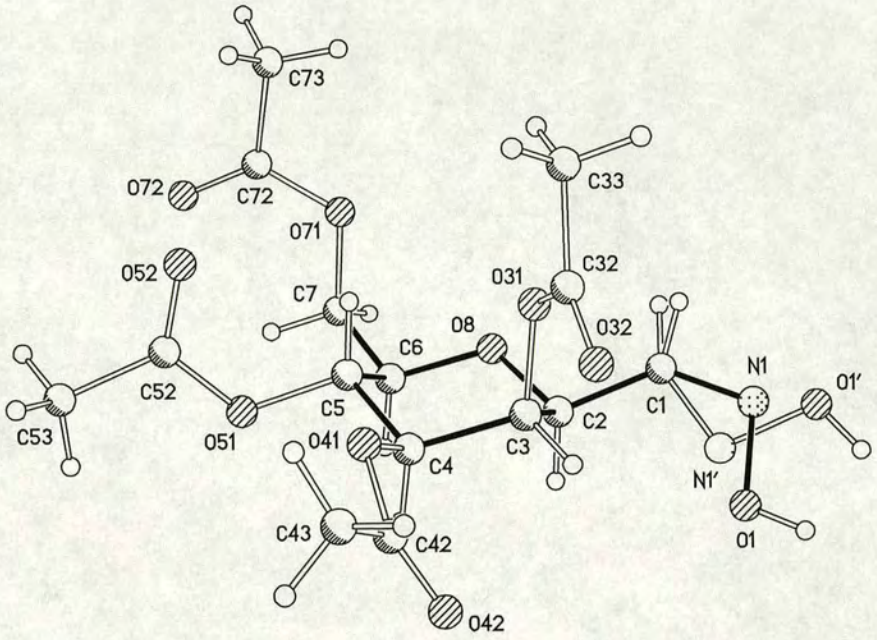


Figure 8

The peracetylated and perbenzylated glucose-derived oximes (**139**) and (**140**), along with the L-fucose-derived oxime (**141**) and the D-mannose-derived oxime (**142**) were prepared similarly from the corresponding pyranosylnitromethanes as summarised in Table 3.

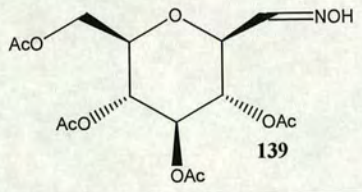
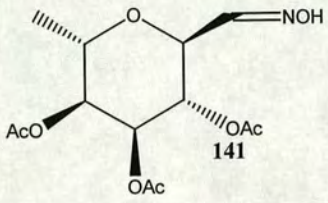
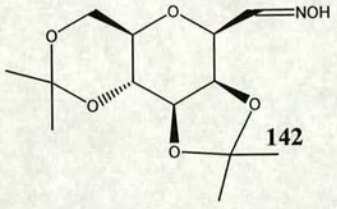
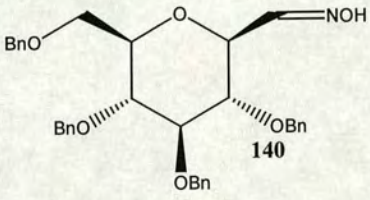
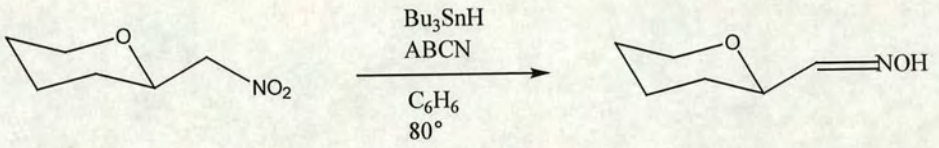
Aldoxime	Yield / (%)	E:Z ratio
 **139**	76	83:17
 **141**	90	88:12
 **142**	80	62:38
 **140**	65	81:19

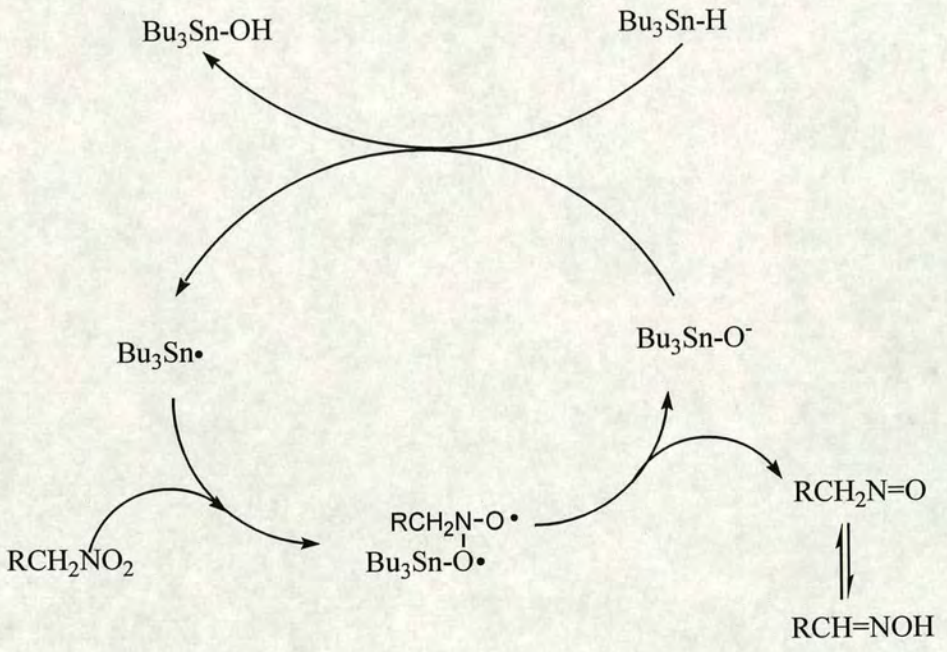
Table 3: Synthesis of pyranosylaldoximes

During the course of this work an alternative route to pyanose-1-carbaldoximes was reported by BeMiller, Petrus *et al.*[134] Whilst attempting the denitration of a selection of per-*O*-acetylated-β-glycopyranosylnitromethanes, it was discovered that the nitro group was not replaced by a hydrogen atom but instead underwent reduction to yield the corresponding oxime (Scheme 52). The conditions employed were heating in benzene for 3-6 hrs in the presence of tributlytin hydride and 1,1'-azobis(cyclohexanecarbonitrile) (ABCN).



Scheme 52

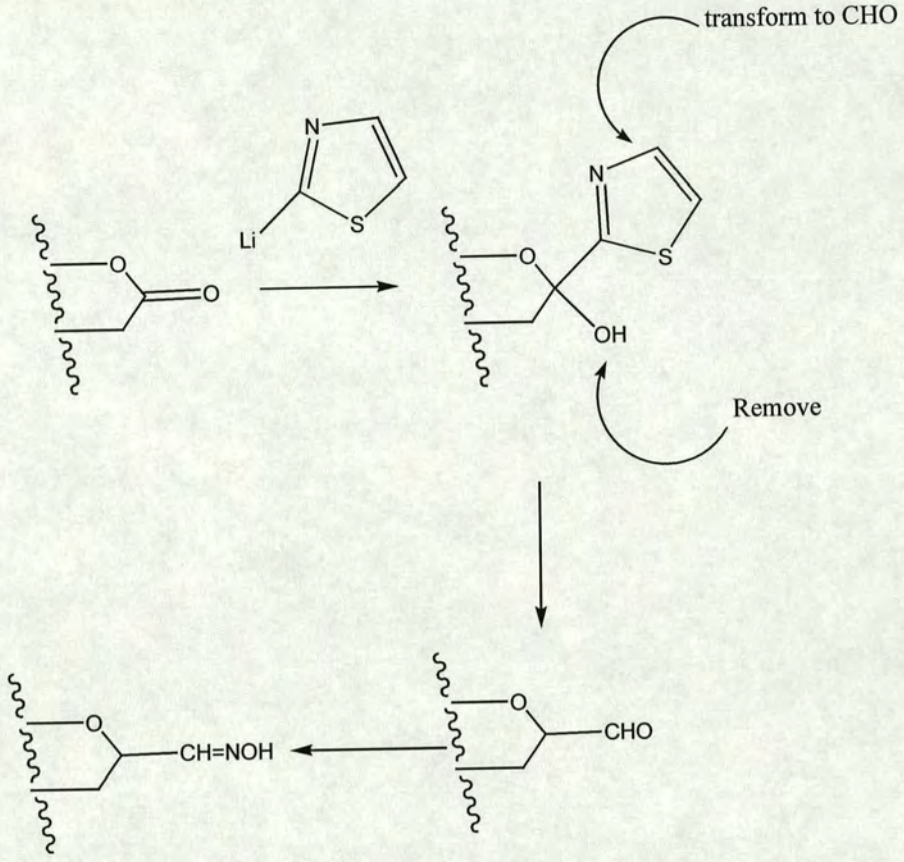
The mechanism for this reaction is believed to involve an addition-elimination, as outlined in Scheme 53, with initial formation of the alkyl(trialkyltinoxy)nitroxyl radical by addition of the tributlytin radical to the nitro compound. Elimination of the nitroso compound followed by isomerisation affords the oxime.



Scheme 53

In comparison to the Bartra route, the two approaches have some similarities. Both have pyranosylnitromethanes as precursors to the oxime and both use tin based reductions. The method of BeMiller *et al*,[134] however, appears to have no major advantage over the Bartra approach[133] providing the oximes in similar yields. Indeed, the elevated temperatures required for the BeMiller method may prove restrictive.

Very recently Dondoni *et al*,[136] in response to our publication describing the reduction of pyranosylnitromethanes using the Bartra approach,[137] have reported the conversion of formyl *C*-glycosides to pyranose-1-carbaldoximes (Scheme 54). Their approach utilises the thiazole route to formyl *C*-glycosides.[101]

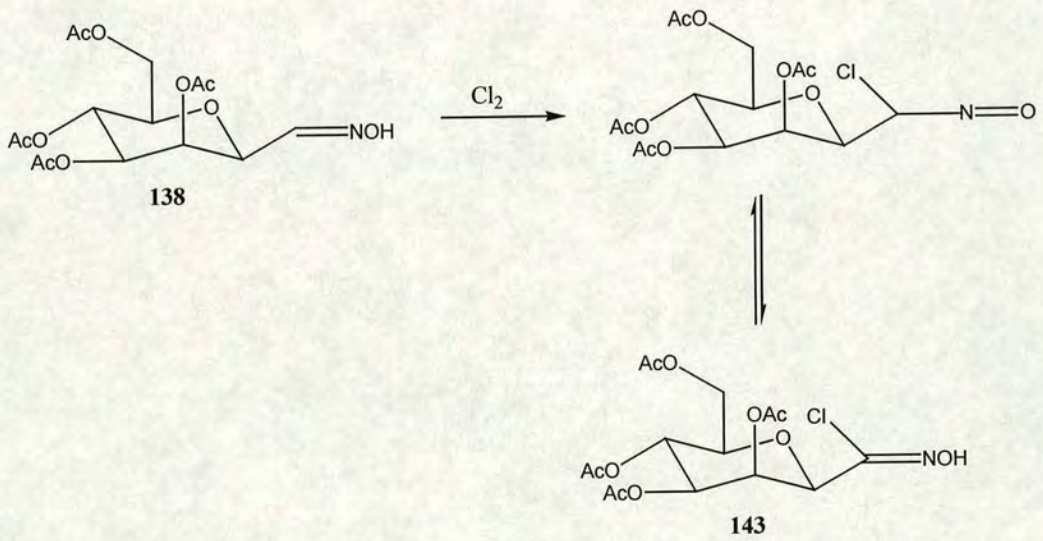


Scheme 54

Dondoni claims this approach is advantageous with respect to the Bartra method as conversion of the formyl *C*-glycoside to the oxime uses the usual mild conditions, hydroxylamine hydrochloride and sodium carbonate, and allows access to both the α- and β-configurations. Access to both configurations is certainly useful, but the methodology described by Dondoni[136] requires a number of extra steps with expensive reagents and forceful conditions, and as a route to β-pyranose-1-carbaldoximes is considered to be less efficient.

2.3.2 Synthesis of pyranosyl hydroximoyl chlorides.

Generation of nitrile oxides from aldoximes often involves conversion to the hydroximoyl chloride by direct chlorination or milder methods such as NCS followed by dehydrochlorination. The synthesis of pyranosyl hydroximoyl chlorides was, therefore, attempted. Direct chlorination was found to work well with formation of the hydroximoyl chloride being achieved by bubbling chlorine gas through the pyranosyl oxime in chloroform at -78°C. As the reaction proceeded there was a characteristic colour change from colourless, through blue, to green, this indicating the presence of the nitroso tautomer. Warming to room temperature and removal of solvent *in vacuo* gave the hydroximoyl chloride (**143**). The presence of the nitroso compound suggests the following mechanism (Scheme 55).



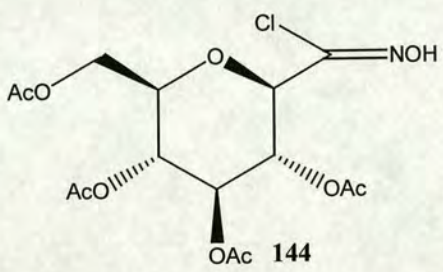
Scheme 55

The mannose derived hydroximoyl chloride (**143**) was synthesised from tetra-*O*-acetyl-*β*-D-mannopyranosyl oxime (**138**) as a single isomer in 87% yield. There are a number of features in the ^{1}H NMR which differ from that of the starting oxime. Firstly, the signal due to of the oxime 1-H is no longer present due to the displacement of hydrogen with chlorine. Thus, the signal for 2-H is simplified to a doublet at around 5.2 ppm, the signal being moved to higher chemical shift due to the introduction of the electron-withdrawing chlorine (2-H at

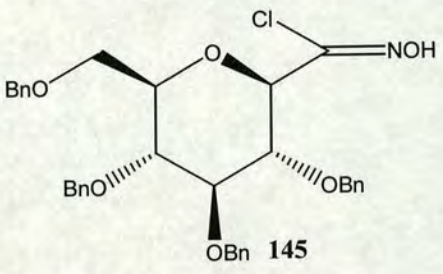
4.3 ppm in oxime). Also, the broad signal due to the NOH moves from 8.53 to 8.80 ppm. There is little change in the pyranose ring proton signals. In the ^{13}C spectrum the peak corresponding to C-1 was shown by the DEPT spectra to have changed from a C-H to a quaternary carbon and moved from 146.1 ppm to 134.6 ppm.

There are two characteristic parent ion signals in the mass spectrum of the compound at 410.08545 amu and 412.06859 amu corresponding to the presence of the two isotopes of chlorine and thus the two molecular formulae: $C_{15}H_{21}NO_{10}{}^{35}Cl$ and $C_{15}H_{21}NO_{10}{}^{37}Cl$. The intensity of the signals suggested a ~3:1 ratio of the products which is in agreement with the natural abundance of the two isotopes.

The peracetylated and perbenzylated glucose-derived compounds (**144**), synthesised from oxime (**139**) and (**145**), synthesised from oxime (**140**) were prepared in 95 % and 82% yields respectively. These compounds were characterised by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry, with both compounds containing the two parent ion peaks as expected.



144



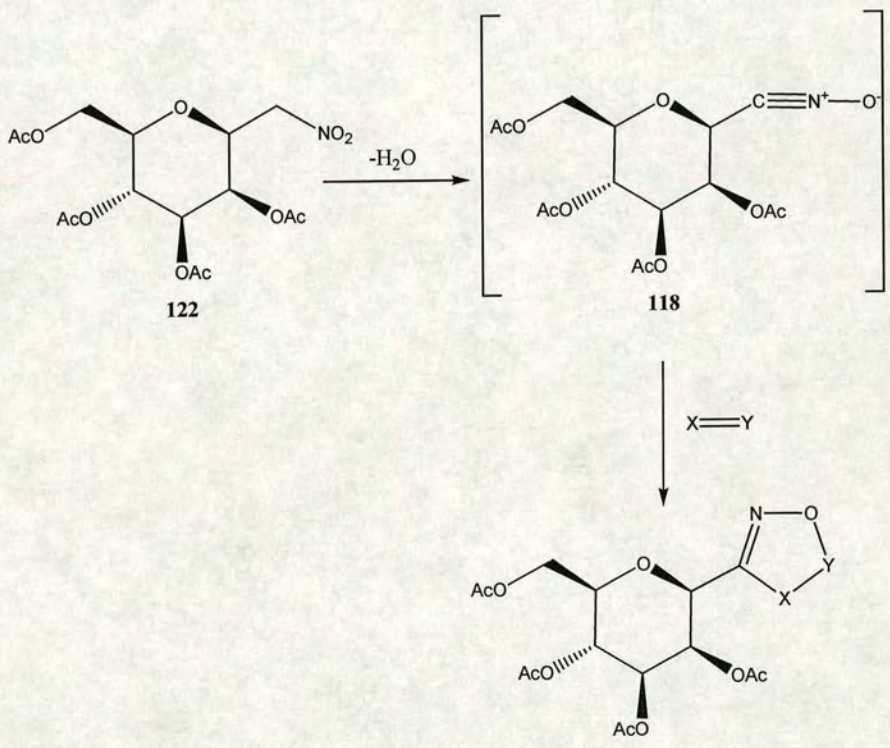
145

2.4 Generation of pyranosylnitrile oxides and cycloaddition reactions

One of the features of nitrile oxides is their tendency to be short lived species, undergoing dimerisation to furoxan if left unreacted. Thus, they are usually generated *in situ* from suitable precursors in the presence of the other reactant, in this case the dipolarophile. Previously, the only method of pyranosylnitrile oxide generation had been *via* the dehydration of pyranosylnitromethanes.[117] This route provides an efficient method of nitrile oxide generation but suffers from a number of disadvantages, thus alternative sources of were investigated, namely the pyranosylaldoxime and hydroximoyl chloride.

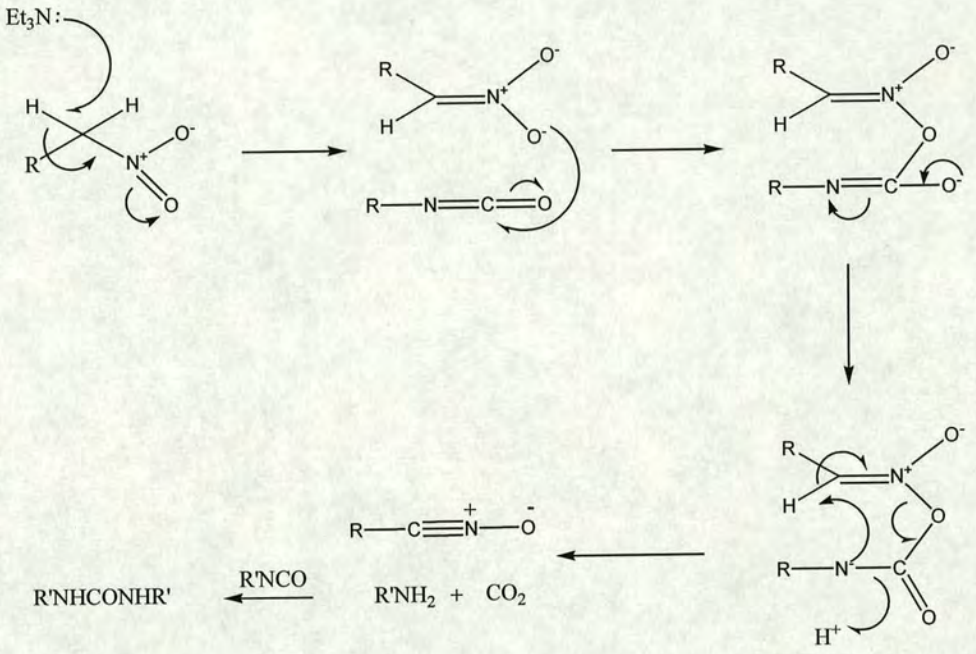
2.4.1 Isocyanate-induced dehydration of pyranosylnitromethanes

The method adopted for dehydration of pyranosylnitromethanes to pyranosylnitrile oxides was based on that of Mukaiyama[9] and is illustrated for the D-mannose derived compound (**122**)(Scheme 56). This involves heating the nitromethyl compound to high temperature (ca 110 °C) for 7 days. Modifications of the approach were made with phenyl isocyanate being replaced by 2,4-tolylene di-isocyanate (TDI) as dehydrating agent. The advantage of using TDI is that the by-product formed is a polymeric urea, which can simply be removed by filtration unlike the diphenyl urea formed when phenylisocyanate is used. Excess 2,4-tolylene di-isocyanate can also be removed by the addition of 1,2-diaminoethane, which reacts to form another poylmeric urea.



Scheme 56

The proposed mechanism for the reaction is shown in Scheme 57 below. It involves initial deprotonation to form the nitronate anion which then reacts with the isocyanate. Collapse of the resulting adduct and loss of CO_2 generates the nitrile oxide along with amine. This latter undergoes further reaction with the isocyanate to form a urea.



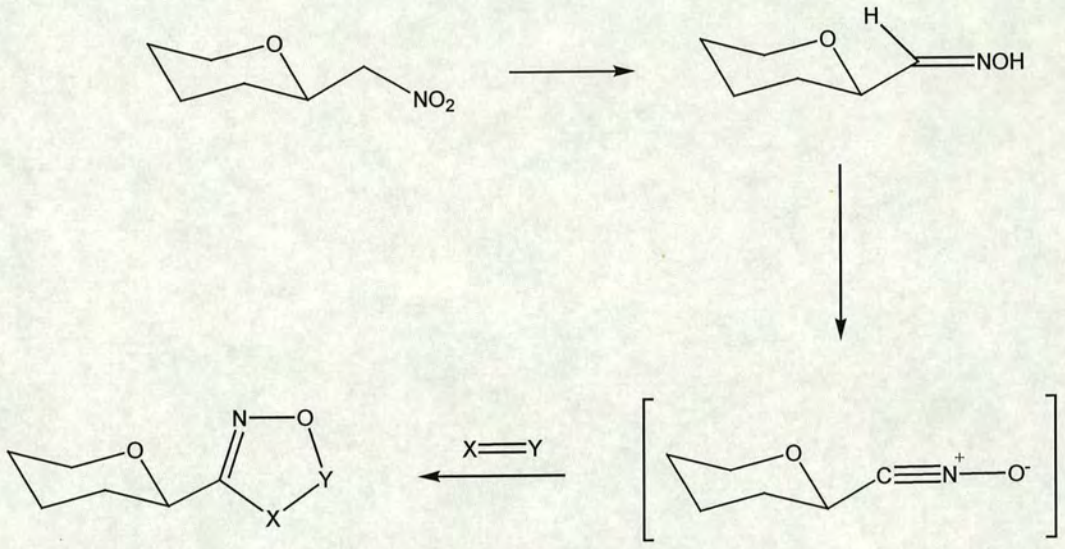
Scheme 57

2.4.2 Alternative routes

The Mukaiyama approach has a number of inherent drawbacks: (1) it requires prolonged reaction times at elevated temperatures, which means that reactions with thermally unstable dipolarophiles and low boiling dipolarophiles (b.p < 60°C) are impossible, (2) the use of isocyanate as dehydrating agent is incompatible with hydroxyl or amino functional groups. Thus, any such groups within either the pyranosylnitromethane or the dipolarophile must be protected to prevent reaction with the isocyanate. To circumvent these problems two other sources have been investigated. The pyranosylaldoxime and hydroximoyl chloride.

2.4.3 Generation of pyranosylnitrile oxides from pyranosylaldoximes.

The conversion of aldoximes to nitrile oxides is a well known reaction. A number of reagents have been used, but the most common is alkaline sodium hypochlorite and the method of Lee *et al*[19] was adopted. The pyranosylaldoxime was generated from the pyranosylnitromethane as described in section 2.3.1 (Scheme 58).

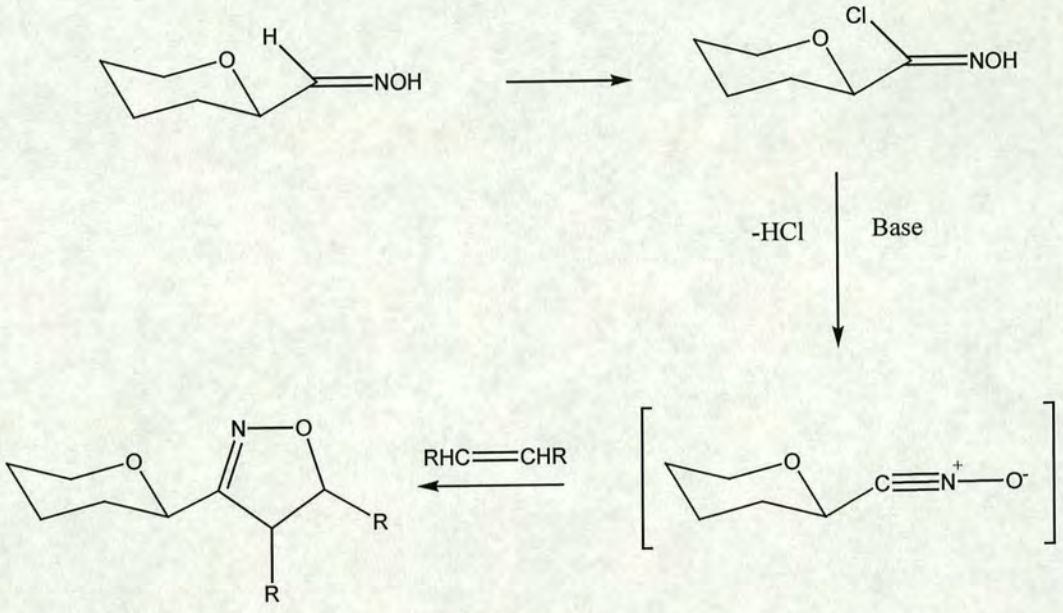


Scheme 58

2.4.4 Conversion of pyranosylhydroximoyl chlorides to pyranosylnitrile oxides

An envisaged problem of using pyranosylaldoximes as precursors to pyranosylnitrile oxides was the lack of control over the rate of nitrile oxide formation. Thus, high levels of dimerisation were possible. With this in mind, a further source of pyranosylnitrile oxides was investigated' the hydroximoyl chloride. The pyranosylhydroximoyl chloride was synthesised from the aldoxime as described in section 2.3.2.

Generation of the nitrile oxide was achieved using classic Huisgen conditions[15] involving base-induced dehydrohalogenation (Scheme 59). An attractive feature of this route is that by controlling the rate of base addition, the rate of nitrile oxide generation can be regulated. Thus, the concentration of nitrile oxide can be kept to a minimum thus, reducing significantly the amount of dimerisation to furoxan.



Scheme 59

Three routes to pyranosylnitrile oxides were now available; by dehydration of the pyranosylnitromethane (method A), oxidation of pyranosylaldoximes (method B) and dehydrohalogenation of pyranosylhydroximoyl chlorides (method C). The three methods are described below.

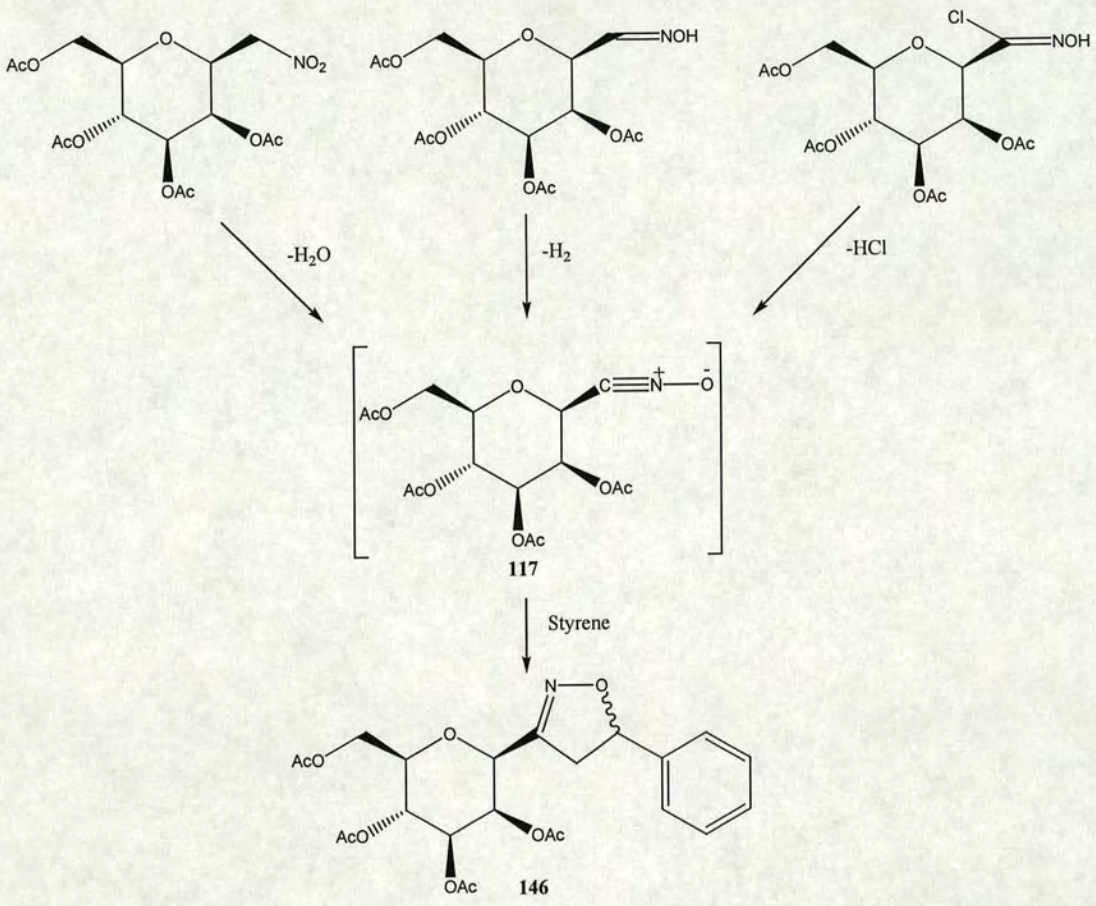
Method A: To the nitrile oxide precursor as a solution in toluene were added TDI, dipolarophile and triethylamine and the reaction mixture heated at reflux for 7 days. The appearance of a yellow polymeric solid, the urea, showed that generation of nitrile oxide was taking place. Excess TDI was removed by reaction with diaminoethane and the resulting polymer and other polymeric ureas removed by filtration. Excess alkene was removed by either evaporation *in vacuo* or chromatography. Where diastereomers were produced the isomer ratio was determined by ^{1}H NMR spectroscopy.

Method B: The conversion of the oxime was carried out in a two phase system of dichloromethane and water, with aqueous sodium hypochlorite as oxidant. The oxime, dipolarophile and a catalytic amount of triethylamine were added and the mixture stirred vigorously. Aqueous sodium hypochlorite was added drop-wise. The product was isolated by extraction into dichloromethane and removal of solvent *in vacuo*.

Method C: The hydroximoyl chloride was dissolved in dry ether along with an excess of the dipolarophile and cooled to 0 °C. A solution of triethylamine in dry ether was added using syringe pump over a 24 hour period. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 hours. These conditions were employed to keep the concentration of the nitrile oxide at a minimum and thus minimise dimerisation to furoxan. Formation of a white precipitate, triethylamine hydrochloride, showed the reaction had taken place. This was removed by aqueous work up. Excess alkene was removed by evaporation *in vacuo* or column chromatography, which was required to remove traces of furoxan.

To investigate the general applicability of all three generation strategies a single dipolarophile, styrene, was reacted with tetra-*O*-acetyl-β-D-mannopyranosylnitrile oxide (**117**) generated by the three methods, A, B and C (Scheme 60). Styrene was chosen due to its high reactivity and ease of removal.

2.4.5 Cycloaddition reaction of 3,4,5,7- tetra-*O*-acetyl-*β*-D-mannopyranosylnitrile oxide (117) with styrene



Scheme 60

Cycloaddition of the D-mannose derived nitrile oxide (**117**) to styrene was carried out using methods A, B and C. In all cases an inseparable mixture of (5R)- and (5S)-5-phenyl-3-(2,3:4,6 tetra-*O*-acetyl-*β*-D-mannopyranosyl)-2-isoxazoline (**146**) was obtained. The yields and isomer ratios are summarised in Table 4. The isomer ratios were determined by ^{1}H NMR by comparison of the signals for the anomeric position and showed the reaction to have little diastereoselectivity. The configuration at the 5-position of the individual isomers was not determined.

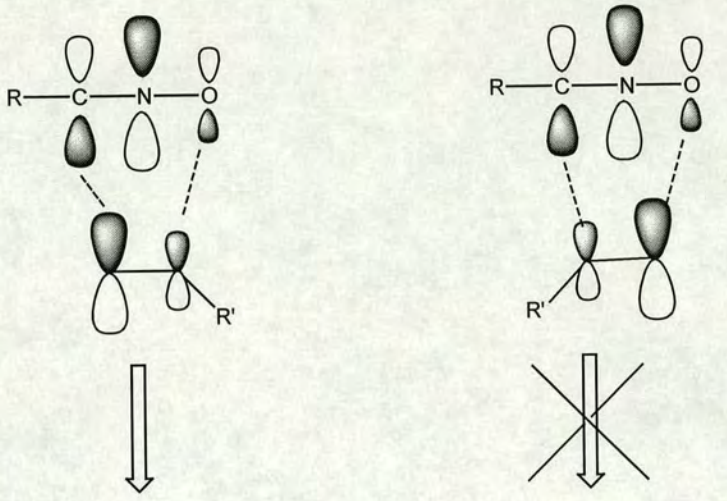
Method of nitrile oxide generation	Yield	Isomer Ratios
Method A-Mukaiyama	95%	56:44
Method B-Hypochlorite	85%	53:47
Method C-Dehydrohalogenation	95%	56:44

Table 4: Summary of (**146**) formation

The ^{1}H NMR spectrum of the products appears as a superimposed combination of the signals of the two diastereoisomers at nearly all positions. Characteristic features include eight singlet peaks between 1.72 and 2.10 ppm corresponding to the four CH_3 groups of the acetate protection in each diastereomer. Peaks at 2.96 and 3.44 ppm correspond to the 4a-H and 4b-H of the isoxazoline ring. These have the geminal coupling to each other and a vicinal coupling to 5-H. Thus both appear as a doublet of doublet for each diastereomer. All ring protons have the expected coupling constants with the β configuration being confirmed by $J_{1,2}$ of 1.3 Hz corresponding to the axial-equatorial arrangement.

The ^{13}C NMR spectrum in conjunction with DEPT experiments confirms the structure. There are two diagnostic signals: (i) a CH_2 signal at 43.2 ppm corresponding to C-4 for the isoxazoline ring and (ii) a quaternary peak at 154.9 ppm due to C-3, the C=N, of the isoxazoline ring. The ^{13}C spectrum also shows the presence of the two diastereomers in similar amounts. Many of the peaks 'double up', for example the C-5 position of the heterocycle shows two peaks of similar intensity at 81.2 and 81.8 ppm.

None of the possible 4-substituted regio-isomer was detected. Thus the cycloaddition appeared to occur regiospecifically. This regiospecificity is observed in most other cycloaddition reactions to mono-substituted alkenes and can be explained by FMO theory (Figure 9). This class of cycloaddition falls into the Sustmann[37] Type III where the dominant interaction is between the LUMO of the dipole and the HOMO of the dipolarophile. Maximum overlap of orbitals is achieved with the dipolarophile in an orientation leading to the 5-substituted product. Steric bulk of the dipolarophile may also disfavour the 4-substituted product.

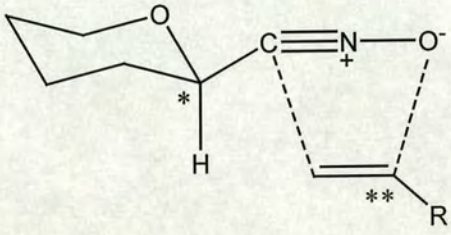


5-Substituted product

4-Substituted product

Figure 9

The lack of disatereoselectivity is not unexpected and there is literature precedent for this observation.[123] One explanation for this lack of diastereoselectivity is the distance between the newly formed chiral centre and existing chiral centre (Figure 10). Thus, there is very little inductive effect.



* existing chiral centre

** newly formed chiral centre

Figure 10

As can be seen in Table 4 the studied reactions proceeded in good yield giving products with similar diastereoisomer ratios. The slight fall in yield for the approach using the pyranosylaldoxime (the hypochlorite method) can be explained by incomplete conversion of the oxime to the nitrile oxide. These results indicate that all three methods of nitrile oxide

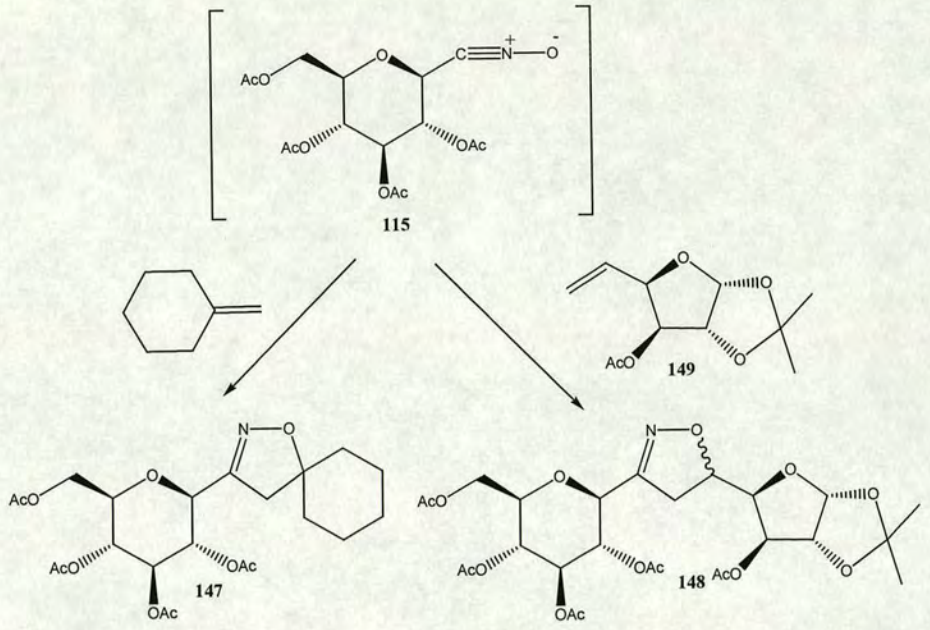
generation are efficient. Although not applicable in all cases, the dehydration of pyranosylnitromethanes provides access to pyranosyl isoxazolines in the least number of steps and thus is often the method of choice. A number of cycloadditions were carried out using this generation strategy to allow the synthesis of interesting isoxazolines and to investigate further the efficiency of the approach.

2.5. Cycloaddition using the Mukaiyama approach

2.5.1 D-Glucose derived nitrile oxides

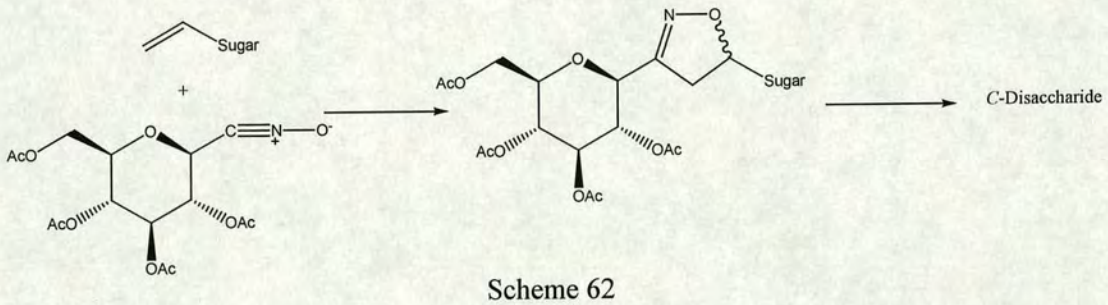
2.5.1.1 Cycloaddition reactions of 3,4,5,7-tetra-*O*-acetyl-*β*-D-glucopyranosyl-formonitrile oxide (115)

The cycloaddition of the glucose derived nitrile oxide (**115**) with methylenecyclohexane was carried out in using method A, but at reduced temperature (90°C) due to the boiling point of the dipolarophile (102-103°C) (Scheme 61). The use of a 1,1-disubstituted alkene led to the formation of a single isomer. The isoxazoline (**147**) was isolated as a white solid in 79% yield. The lack of diastereomers gave much simplified spectra enabling easier assignment. In the ^{1}H NMR spectrum the 4a-H and 4b-H of the isoxazoline ring appear as doublets with a geminal coupling constant of 17.1 Hz, whilst the cyclohexane ring protons appear as complex set of multiplets between 1.22 and 1.67 ppm. The sugar ring protons are at similar chemical shifts with almost identical couplings to those of the nitrile oxide precursor with the β-configuration is confirmed by the $J_{1',2'}$ of 10.0 Hz caused by the diaxial arrangement. The main diagnostic peaks in the ^{13}C spectrum relate to the isoxazoline ring with signals at 42.2, 87.5 and 154.1 ppm corresponding to the CH_2 at C-4, the quaternary at C-5 and the C=N quaternary at C-3, respectively.



Scheme 61

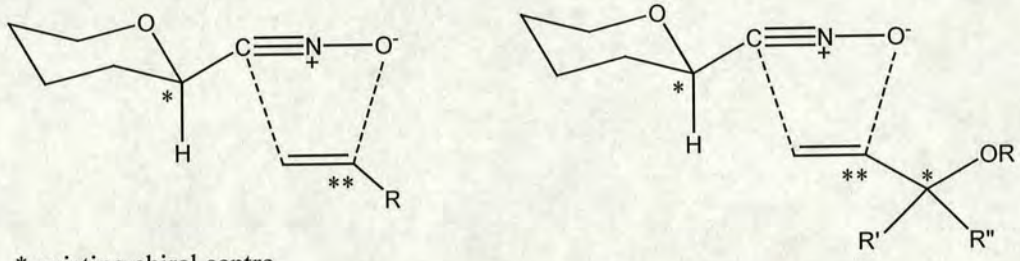
Within the group the nitrile oxide / isoxazoline route has been used as a method of *C*-disaccharide synthesis.[117] A prerequisite for this is the use of sugar-derived alkenes as the dipolarophile (Scheme 62).



Scheme 62

With the possibility of *C*-disaccharide synthesis in mind the cycloaddition of the glucose-derived nitrile oxide (**115**) with the glucose-derived alkene, 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**149**) was carried out using method A. The sugar alkene (**149**), supplied by A. R. March,[123] was synthesised in 4 steps from the commercially available 1,2:5,6-di-*O*-isopropylidene-D-glucose. The product (**148**) was isolated as a mixture of diastereomers from unreacted alkene by column chromatography in 79% overall yield and the isomer ratio determined by ^{1}H NMR to be 75:25. The major

isomer was isolated by repeat recrystallisation from ethanol. This isomer, assigned the *eyrtho* stereochemistry, was characterised by ^{1}H and ^{13}C NMR as well as comparison with an authentic sample. An interesting feature of the ^{1}H NMR is the $J_{2\text{-}3}$ value of 0 Hz, consistent with the expected dihedral angle of ~90°. Unlike the cycloaddition reaction with styrene, significant diastereoselectvity is observed for this example. This π-facial selectivity, which leads to the *erythro* product being favoured, is known for chiral enol ethers[138] and has been explained using Houk's 'inside alkoxy effect'.[139] The lack of diastereoselectivity seen for the styrene adduct has been explained previously (section 2.5) and an explanation for the significant selectivity for the reaction of the sugar alkene involves the proximity of the newly formed chiral centre to the existing chiral centre (Figure 11). Thus, there is a greater influence on the stereochemical outcome of the reaction.



* existing chiral centre

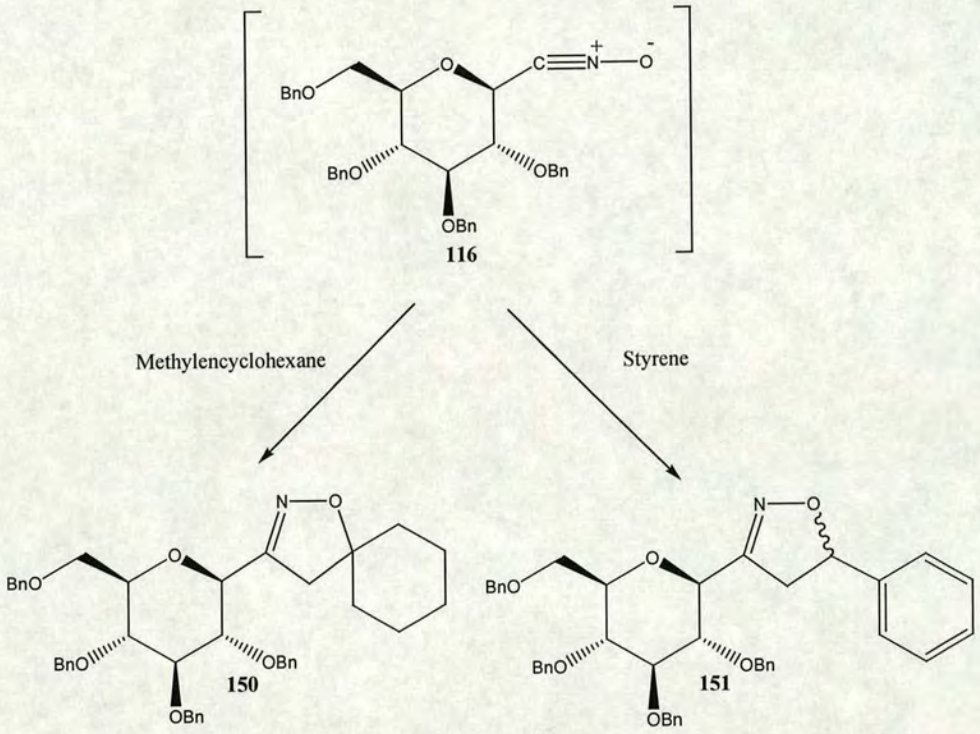
** newly formed chiral centre

Figure 11

2.5.1.2 Cycloadditions reactions of 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylformonitrile oxide (116)

Generation of the novel 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylformonitrile oxide (**116**) was studied by cycloaddition of (**116**) with methylenecyclohexane using method A (Scheme 63). Methylenecyclohexane was chosen due to its reactivity, ease of removal on completion of reaction and the lack of isomerism in the product. Isoxazoline (**150**) was isolated by dry flash chromatography from unidentified impurities as a clear oil, which solidified on standing, in 80% yield. The ^{1}H NMR showed the presence of the benzyl protection with signals between 4.57 and 4.99 ppm corresponding to the four CH_2 groups and between 7.18 and 7.35 ppm indicating the four phenyl rings. A signal at 2.71 due to two overlapping

doublets was assigned to the 4a-H and 4b-H of the isoxazoline ring, whilst the $J_{1\text{-}2}$ value of 9.6 Hz confirmed the β-configuration. The sugar ring protons found in the range 3.45 to 3.88 ppm were poorly resolved, making full assignment impossible. In the ^{13}C NMR spectra the signals due to the C-3, C-4 and C-5 positions of the isoxazoline ring proved diagnostic. These appeared at 156.2, 48.9 and 86.6 ppm respectively. The compound was further characterised by high resolution mass spectroscopy. As expected, the reaction was regiospecific.



Scheme 63

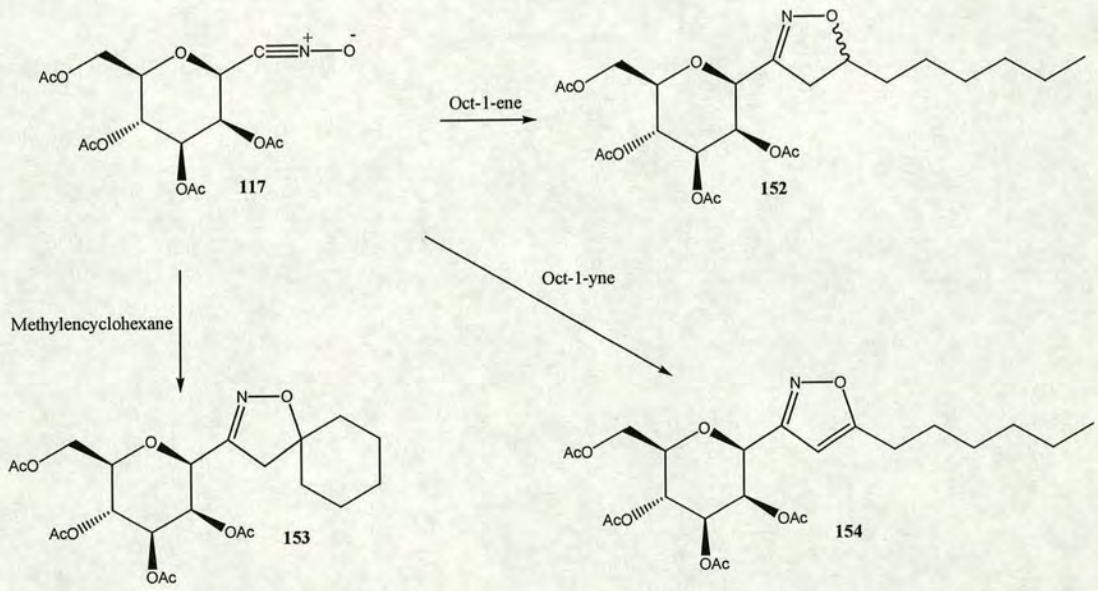
The glucose-derived nitrile oxide (**116**) was also reacted with styrene using method A (Scheme 63). The products (**151**) were obtained as a pair of diastereomers (80%) as a yellow oil which solidified on standing. The isomer ratio was determined by ^{13}C NMR to be approximately 53:47 and (**151**) was identified by ^{1}H and ^{13}C NMR with diagnostic peaks in ^{13}C spectrum corresponding to the isoxazoline ring carbons.

2.5.2 D-Mannose derived nitrile oxides

Previous work within the group had concentrated on D-glucose and D-xylose-derived nitrile oxides. To investigate further the reaction of pyranosylnitrile oxides, cycloaddition reactions of mannose-derived nitrile oxides with various dipolarophiles were investigated.

2.5.2.1 Cycloadditions of 3,4,5,7-tetra-*O*-acetyl-*β*-D-mannopyranosyl-formonitrile oxide (117)

The cycloaddition reactions of the mannose-derived nitrile oxide (**117**) with oct-1-ene and methylenecyclohexane were carried out using method A (Scheme 64). Reaction with oct-1-ene gave a pair of inseparable diastereomers (**152**) in a 51:49 ratio as determined by ^{13}C NMR spectroscopy. The combined yield was 72%. Reaction with methylenecyclohexane afforded isoxazoline (**153**) (88%). All products were characterised by ^{1}H and ^{13}C NMR spectroscopy and showed $J_{1'-2'}$ values of ~ 1.5 Hz characteristic of the β-configuration.

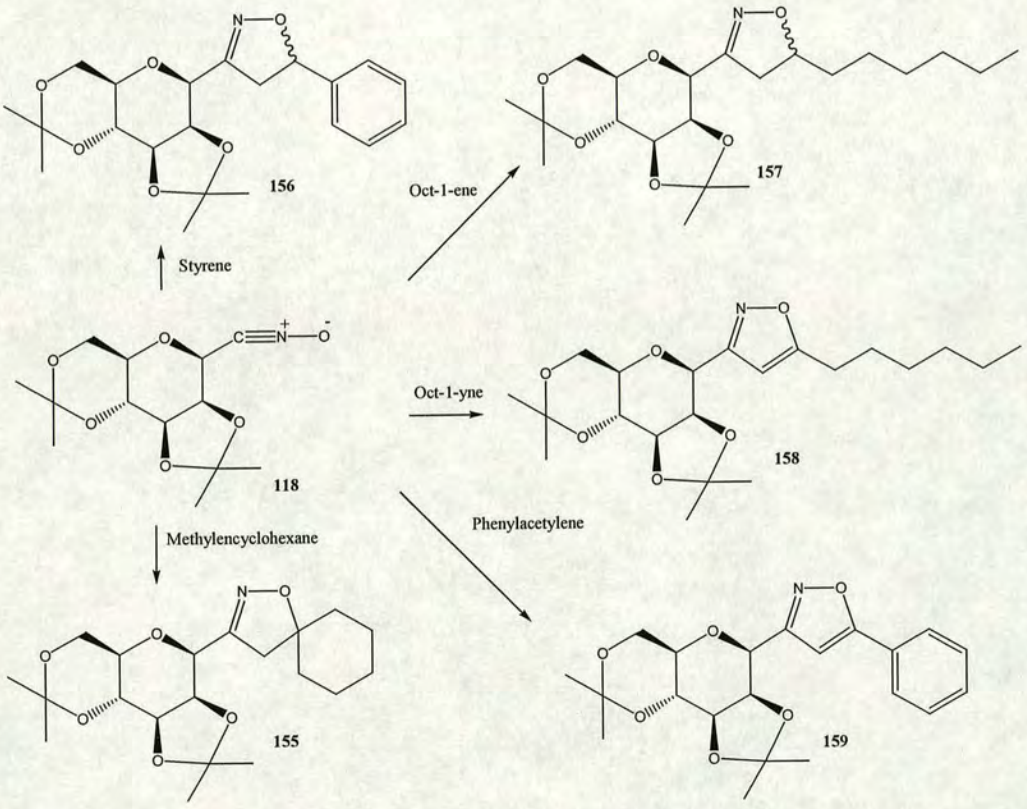


Scheme 64

The cycloaddition of the mannose-derived nitrile oxide (**117**) with oct-1-yne was carried out using method A to determine whether the route was applicable to the synthesis of isoxazoles. The isoxazole (**154**) was obtained as a clear oil in 78% yield and, as expected, only one regioisomer was formed. The ^{1} H NMR contained a characteristic singlet at 5.97

ppm due to the 4-H of the isoxazole ring. There is a large contrast between the position of the 4-H signal in this isoxazole and the corresponding isoxazoline (5.97 cf ~2.8 ppm). The ^{13}C spectrum displayed the same effect with the 4-CH of the isoxazole at 99.5 ppm compared, to 45.4 ppm for the CH_2 group in the corresponding isoxazoline. The two other isoxazole ring carbons gave peaks at 159.9 ppm and 174.0 ppm due to C-3 and C-5 respectively.

2.5.2.2 Cycloadditions of 3,4:5,7-di-*O*-isopropylidene-*β*-D-mannopyranosyl-formonitrile oxide (118) (Scheme 65)



Scheme 65

The cycloaddition reaction of methylenecyclohexane with the novel mannose-derived nitrile oxide (**118**) was carried out using method A to investigate the applicability of nitromethylcompound (**130**) as a precursor. Isoxazoline (**155**) was isolated in 84% yield as a single regioisomer. The ^1H spectrum contained four singlets between 1.28 – 1.50 ppm corresponding to the CH_3 of the isopropylidene protection. The usual overlapping doublets were seen at 2.80 ppm due to the 4a- and 4b-H protons of the isoxazoline ring with a

geminal coupling of 17.2 Hz and, the β-stereochemistry was confirmed by the $J_{1,2}$ coupling of 2.7 Hz. This value is larger than that for the acetate protected pyranosyl isoxazoline, indicating the flattening of the ring caused by the presence of the fused 1,3-dioxane and 1,3-dioxalane rings. The coupling of the ring protons is similar to the parent nitromethyl compound denoting the slightly flattened $^4C_1$ conformation. The ^{13}C NMR spectrum showed the presence of four methyl groups from the acetal protection at 18.6, 26.1, 28.2, and 28.8 ppm. The signals at 18.6 and 28.8 are assigned to the 1,3-dioxane ring whilst the other two at 28.2 and 28.8 are due to 1,3-dioxolane.[128] There is significant differences in the chemical shifts of the ketal quaternary peaks with the 1,3-dioxane peak at 99.5 ppm whilst the 1,3-dioxolane is found at 109.8 ppm. The other signals in the spectrum are as expected and include a characteristic peak at 156.6 ppm due to the C=N of the isoxazoline.

Further cycloaddition reactions of the mannose-derived nitrile oxide (**118**) with styrene, oct-1-ene, oct-1-yne and phenylacetylene were carried using method A and yielded isoxazolines (**156**) and (**157**) as mixtures of diastereomers, and isoxazoles (**158**) and (**159**) respectively. The results are summarised in Table 5.

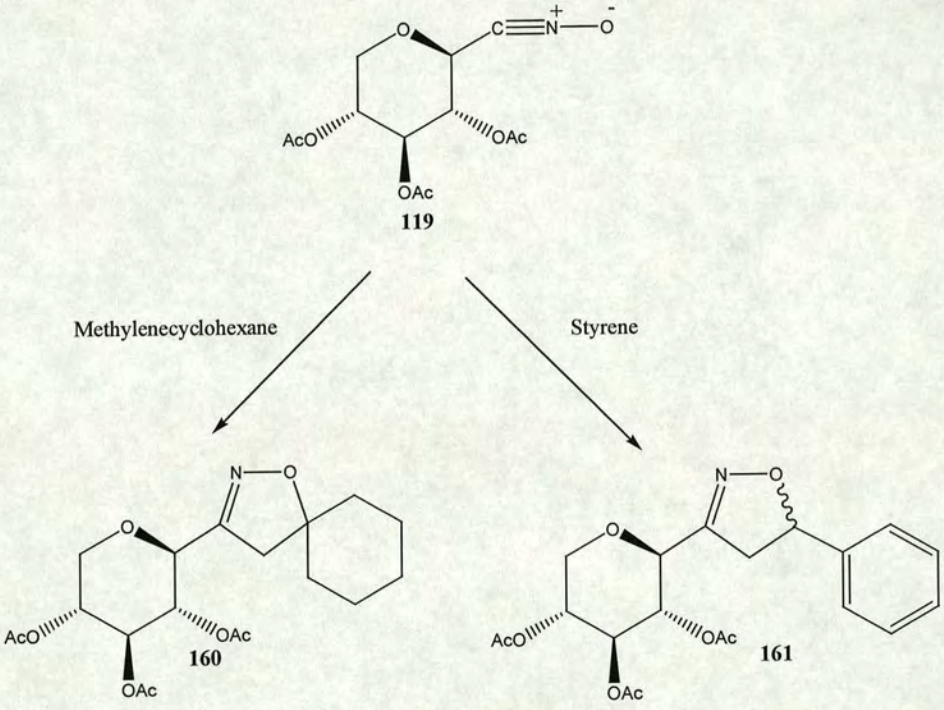
Compound	Yield / %	Isomer ratio
(**156**)	79	53:47
(**157**)	53	56:44
(**158**)	80	n/a
(**159**)	80	n/a

Table 5: Formation of cycloadducts (**156**) - (**159**)

2.5.3 Cycloadditions of 3,4,5-tri-*O*-acetyl-*β*-D-xylopyranosyl-1-nitrile oxide

Due to the relatively high yields for the formation of 3,4,5-tri-*O*-acetyl-*β*-D-xylopyranosylnitromethane, its use as a precursor to nitrile oxides was adopted. Thus, the xylose-derived nitrile oxide (**119**) was generated and reacted with methylenecyclohexane employing the conditions outlined in method A. Isoxazoline (**160**) was obtained as a white solid in 78% yield. The ^{1}H NMR showed three singlets between 2.01 and 2.04 ppm corresponding to the CH_3 groups of the acetate protection. The 4a- and 4b-H of the isoxazoline ring at 2.73 ppm show the characteristic geminal coupling of 17.2 Hz. A triplet

at 3.36 ppm and a doublet of doublets at 4.14 ppm correspond to the 5a'- and 5b'-H of the pyranose ring and, the β-conformation is confirmed by the $J_{1',2'}$ value of 9.9 Hz. The ^{13}C NMR showed three signals at 21.0 to 21.1 ppm and three more at 170.2 to 170.3 ppm due to the acetate protection. The diagnostic isoxazoline signals occurred at 42.8, 87.8 and 154.8 corresponding to C-4, C-5 and C-3 respectively.

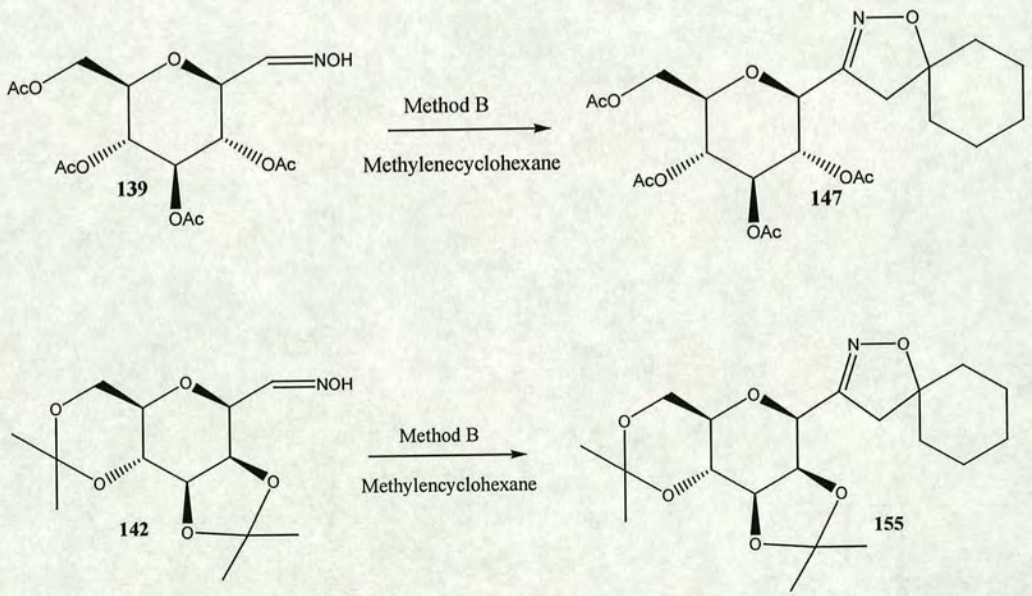


Scheme 66

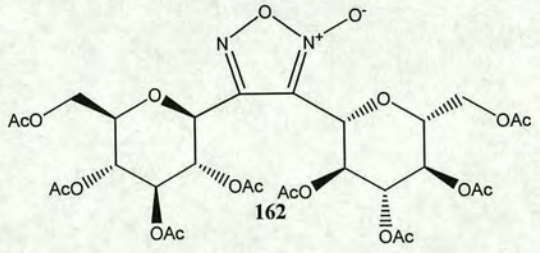
The cycloaddition of the xylose-derived nitrile oxide (**119**) with styrene gave a pair of diastereomeric isoxazolines (**161**) in 60% yield. The isomer ratio was determined by ^{13}C NMR spectroscopy to be 55:45 with (**161**) being identified by ^{1}H and ^{13}C NMR spectroscopy.

2.6 Generation of pyranosylnitrile oxides from pyranosylaldoximes and subsequent cycloaddition reactions

To investigate further the use of the pyranosylaldoxime as a precursor to the pyranosylnitrile oxide, the cycloaddition reactions of 3,4,5,7-tetra-*O*-acetyl-*β*-D-glucopyranosyl-1-nitrile oxide (**115**) with methylenecyclohexane and 3,4,5,7-di-*O*-isopropylidene-*β*-D-mannopyranosyl-1-nitrile oxide (**118**) with methylenecyclohexane were attempted using the conditions described in method B (Scheme 67). Isoxazoline (**147**) and isoxazoline (**155**) were obtained in 62 % and 52%, respectively, and were characterised by comparison with authentic samples. In both cases considerable amounts of furoxan by-product were obtained (e.g. furoxan (**162**) form (**115**)). This confirms the expected drawback of pyranosylaldoximes as precursors to pyranosyl nitrile oxides. As there is no means of controlling the rate of nitrile oxide formation, high concentrations can occur, favouring dimerisation to furoxan.



Scheme 67

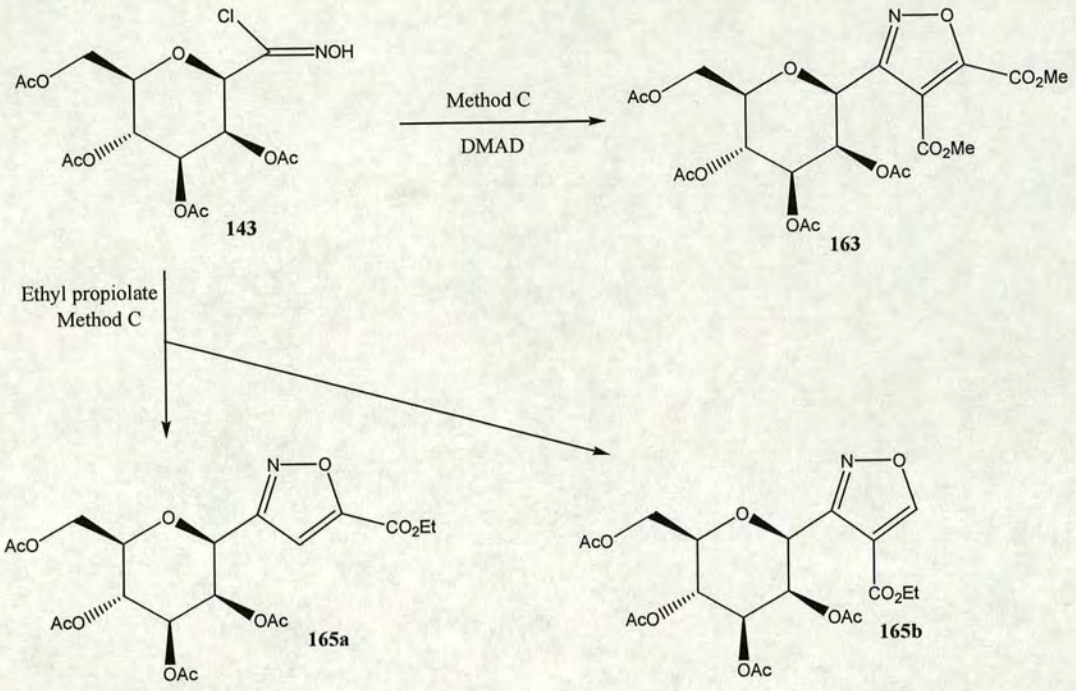


2.7 Generation of pyranosylnitrile oxides from pyranosylhydroximoyl chlorides and subsequent cycloaddition reactions

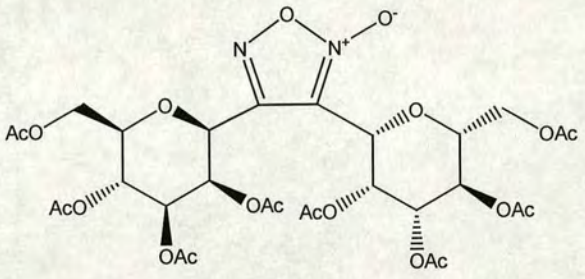
The high levels of dimerisation by-product observed using the pyranosylaldoximes as precursor made the hydroximoyl chloride precursor an attractive alternative source of nitrile oxides. As generation is achieved using base catalysed dehydrohalogenation, slow addition of base would lead to low concentrations of nitrile oxide and thus reduce dimerisation. To test this hypothesis the cycloaddition reactions of 3,4,5,7-tetra-*O*-acetyl-*β*-D-mannopyranosyl-1-nitrile oxide (**117**), generated from the hydroximoyl chloride precursor, with DMAD, ethyl propiolate, oct-1-ene, cyclohex-2-enone, ethyl cyanoformate, phenylacetylene and allyl alcohol were attempted.

2.7.1 Cycloadditions of 3,4,5,7-tetra-*O*-acetyl-*β*-D-mannopyranosyl-1-nitrile oxide (117)

The tendency for DMAD to polymerise at elevated temperatures prevented its use in cycloaddition reactions using the Mukaiyama procedure.[9] It had also proved problematic when reacted with the aldoxime precursor.[123] Thus, using method C, the cycloaddition of the D-mannose based nitrile oxide (**117**) with DMAD was undertaken (Scheme 68). Isoxazole (**163**), as a yellow oil (70%), was isolated from furoxan by-product (**164**) (15%) by chromatography. In the ^{13}C spectrum, the isoxazole peaks at 156.1 and 114.5 for C-3 and C-4 agree with expected values.[123] The C-5 peak is among those of the methyl esters (CO_2CH_3) around 160 ppm.



Scheme 68



164

Unlike DMAD, ethyl propiolate is asymmetric and two regioisomeric adducts are possible. To investigate the regioselectivity of the cycloaddition reaction, the cycloaddition of the D-mannose based nitrile oxide (**117**) with ethyl propiolate was carried out using method C. Three products were isolated from the reaction mixture spots. Furoxan (**164**) was obtained in 10% yield along with an inseparable pair of regioisomers, 3-(2,3:4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-5-ethylester-isoxazole (**165a**) and 3-(2,3:4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-4-ethylester-isoxazole (**165b**) in a combined 79% yield. The ratio of regioisomers was determined by comparison of the integrals in the ^{1}H NMR of the 4-H and 5-H isoxazole ring protons for the 2 isomers. The signals were at 7.25 and 6.37 ppm and the ratio was determined to be 7:1 in favour of the 5-substituted product. The product was

characterised by ^{1}H and ^{13}C NMR spectroscopy and by high-resolution mass spectrometry. There is literature precedent for such regio-isomersim.[140] The cycloaddition of benzonitrile oxide and methyl propiolate exhibits two regioisomers in a 72:28 ratio.[140] Previous cycloadditions reactions attempted had been regioselective. The reason for regioisomerism when ethyl propiolate is used as dipolarophile can be explained by considering the Sustmann[37] classification. The introduction of an electron withdrawing group (W) lowers the energy of both the HOMO and the LUMO of the dipolarophile. Thus, as well as the dominant Sustmann type III interaction which affords the 5-substituted product, interaction of the LUMO-dipolarophile and HOMO-dipole (Sustmann type II) is now possible allowing some 4-substituted product to be observed (Figure 12). The low steric demand of the ester group also favours formation of the 4-substituted product.

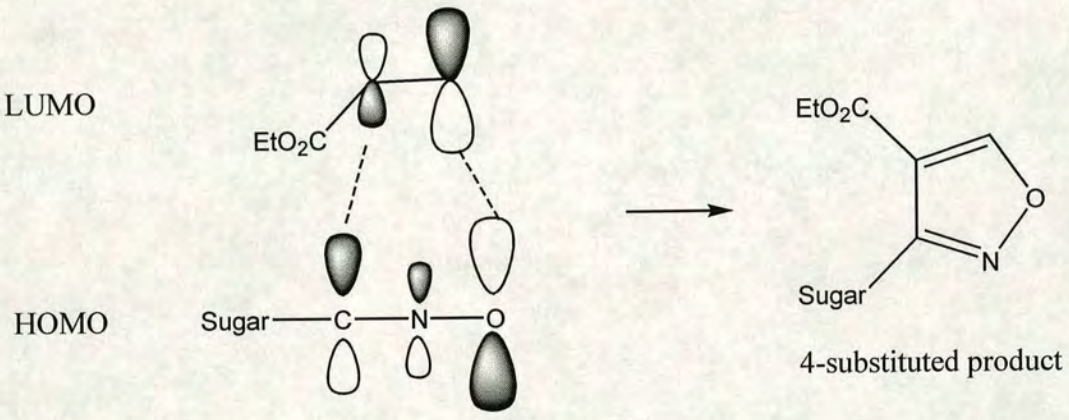
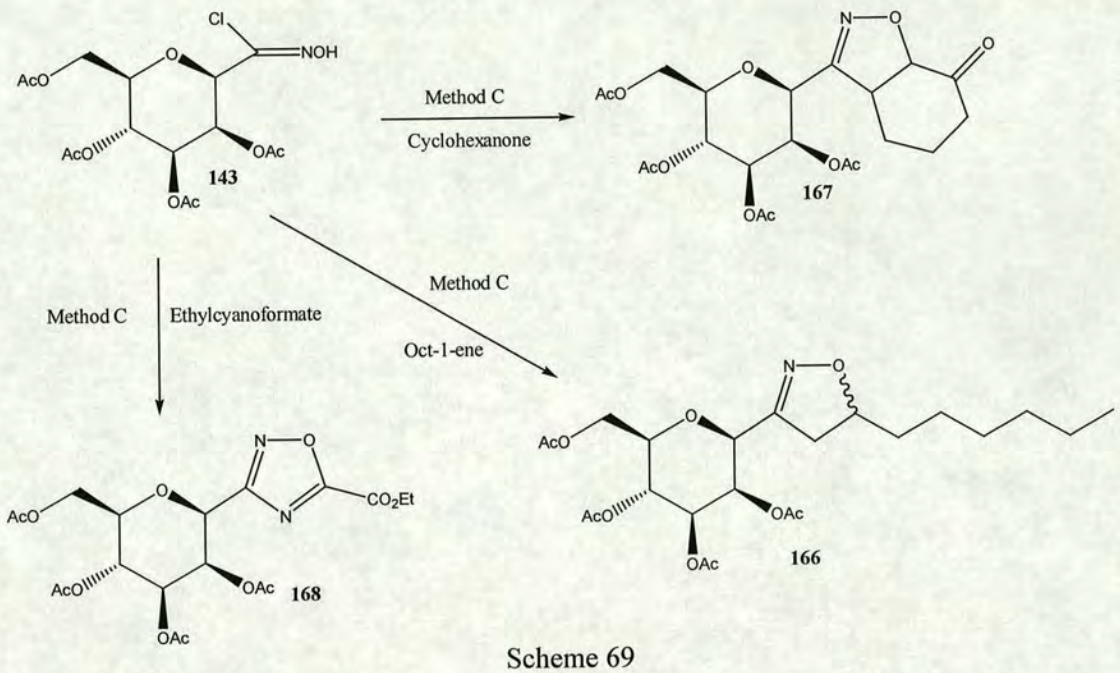


Figure 12

The cycloaddition of the D-mannose based nitrile oxide (**117**) with oct-1-ene (Scheme 69) was carried out using method C. A pair of inseparable diastereomeric isoxazolines (**166**) were isolated in 87% combined yield, in a 51:49 ratio as determined from the ^{13}C spectrum with characterisation of (**166**) achieved by ^{1}H and ^{13}C NMR spectroscopy as well as comparison with an authentic sample. Furoxan (**164**) was obtained as a by-product in a 11% yield.

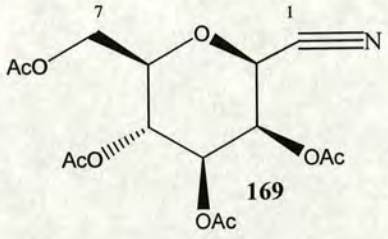


Scheme 69

A more in-depth study on the regioselectivity of cycloaddition reactions was achieved by reaction of the D-mannose based nitrile oxide (**117**) with cyclohex-2-enone, carried out using method C. A pair of inseparable diastereomeric isoxazolines (**167**) were isolated from an unknown side product in 79% yield, but no regioisomerism was detected. The diastereoisomer ratio was determined to be 55:45. The ^{1}H NMR of the compound shows a doublet at 3.75 ppm due to the 7a-H proton, which only couples to the 3a-H proton. The other protons from the cylohexanone ring appear as a complex multiplet between 1.79 and 2.54 ppm, whilst the 3a-H appears as a multiplet at 4.87 ppm. The ^{13}C NMR shows two diagnostic C-H peaks at 59.6 and 81.8 ppm corresponding to C-3a and C-7a of the isoxazoline ring. There is also the C=N at 152.9 ppm and a peak at 205.7 ppm due to carbonyl group on the cyclohexyl ring.

Previous attempts within the group to react pyranosylnitrile oxides with ethyl cyanoformate had failed. Therefore, the cycloaddition of the D-mannose based nitrile oxide (**117**) with ethyl cyanoformate was attempted, using method C. Although a small amount of what was believed to be the desired product was obtained the dominant product was furoxan (**164**) in 58% yield. This indicates the low reactivity of ethyl cyanoformate towards pyranosylnitrile oxides. In an attempt to form the cycloadduct, the reaction was repeated at elevated

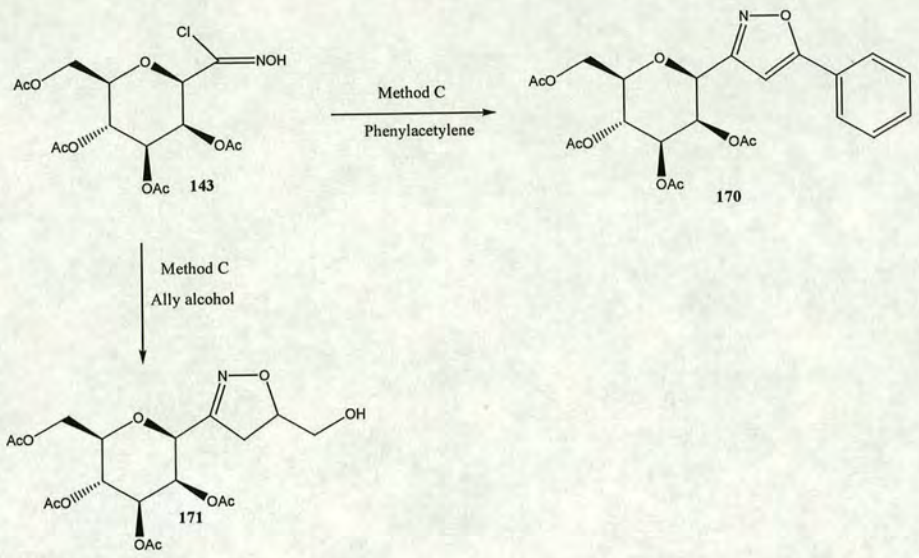
temperature. 3,4,5,7-Tetra-*O*-acetyl-*β*-D-mannopyranosyl hydroximoyl chloride (**143**) was added to the dipolarophile in THF, heated to 70°C and then triethylamine in THF added over a 24 hour period. The 1,2,4-oxadiazole (**168**) was obtained as a single isomer in a 15% yield but the dominant product was again furoxan (**164**) obtained in 65% yield. (**168**) was identified by ^{1}H NMR which showed peaks at 1.43 ppm and 4.50 ppm for the CH_3CH_2 group and movement of the 1'-H signal to higher chemical shift (4.6 – 5.0 ppm) possibly due to the increased inductive effect of the heterocyclic ring. In the ^{13}C spectrum there where peaks at 14.4 and 63.0 ppm due to the CH_2CH_3 group and at 125.9 and 154.0 due to C-5 and C-3 of the heterocyclic ring.



169

To determine if temperature had any effect on the regioselectivity of reactions, D-mannose derived nitrile oxide (**117**) was reacted with cyclohex-2-enone at elevated temperature using the method described for ethyl cyanoformate. It was hoped that an increase in reaction temperature may favour the formation of the 4-substituted isomer. The TLC of the reaction mixture showed three spots. After chromatography two main products were isolated: the furoxan (25%) and a white crystalline solid which was determined to be the pyranosylnitrile (**169**) (58 %). The formation of these nitriles as by-products has been seen previously in the group although no explanation for there formation has been forthcoming. The nitrile was characterised by ^{1}H and ^{13}C NMR.

D-Mannose derived nitrile oxide (**117**) was reacted with phenylacetylene in accordance with the method C (Scheme 70). The isoxazole (**170**) was obtained as a white crystalline solid in 37% yield whilst furoxan (**164**) was also obtained in a 35% yield. The ^{1}H NMR showed a diagnostic singlet at 6.56 ppm due to the 4-H of the isoxazole and the ^{13}C spectrum showed peaks at 160.7, 98.3 and 169.9 ppm due to C-3, C-4 and C-5 of the isoxazole ring.



Scheme 70

One of the inherent drawbacks of the Mukaiyama route to nitrile oxides is the use of isocyanate-dehydrating agents due to their possible reaction with any hydroxyl and amine functional groups in the reagents. To test the tolerance of the hydroximoyl chloride approach to functionality, the D-mannose derived nitrile oxide (**117**) was reacted with allyl alcohol using method C. Three products were isolated by chromatography, (**171**) as a mixture of inseparable diastereomers in approximately 50:50 ratio and 30% overall yield and furoxan (**164**) (14%). The ^{1}H NMR of the product showed the characteristic signals at around 3.0 ppm due to the 4a-H and 4b-H protons of the isoxazoline ring and a broad singlet at 6.96 ppm due to the OH. In the ^{13}C NMR there were the characteristic isoxazoline peaks at 156.6, 36.9 and 81.0 ppm for C-3, C-4 and C-5 respectively.

2.7.2 Summary

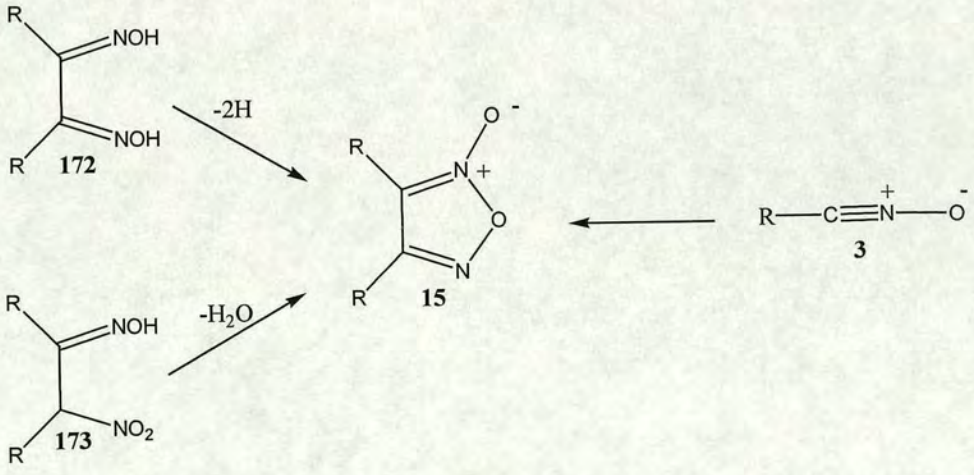
The scope of cycloaddition reactions of pyranosylnitrile oxides has been increased with the introduction of the two new precursors, pyranosylaldoximes and pyranosylhydroximoyl chlorides. Both provide efficient routes to the nitrile oxide with the hydroximoyl chloride approach allowing minimisation of furoxan production. The Mukaiyama approach is also an efficient method of nitrile oxide generation and does not suffer from furoxan formation but is limited by its incompatibility with certain dipolarophiles.

2.8 1,2,5-oxadiazole 2-oxides (furoxan) chemistry

One of the inherent drawbacks of nitrile oxide cycloaddition chemistry is the tendency of the nitrile oxides to dimerise to furoxans. Using the Mukaiyama conditions minimises dimerisation, but this method is not applicable to all dipolarophiles. Even when concentrations of nitrile oxide are kept to a minimum, as in the case when pyranosyl hydroximoyl chlorides are used as precursor, significant amounts of furoxan may still be formed. However, on closer inspection, this "unwanted" by-product may have synthetic utility. For example, the furoxan, like the isoxazoline ring is open to chemical manipulation, which could lead to novel carbon bridged disaccharides.

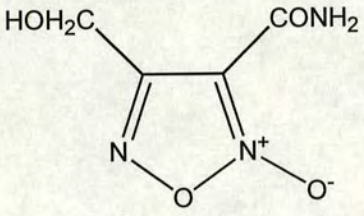
Furoxans have been known since the 1850's and much attention has been paid to structure determination, development of preparative methods and examining their reactions.[25]

There are three main preparative routes to furoxans (**15**): *via* oxidative cyclisation of 1,2-dioximes (**172**),[141] the dehydration of α-nitroketoximes[142] (**173**) with e.g. chlorosulfonic acid and, for symmetrically substituted furoxans, the dimerisation of nitrile oxides[25] (**3**) (Scheme 71). As the dimerisation of nitrile oxides is known to work well and, with suitable carbohydrate dioxime and nitroketoxime precursors not readily available, this route was adopted.

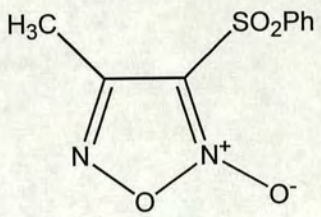


Scheme 71

Furoxans show a wide range of biological activity, including potential as nitric oxide donors.[143] A variety of NO-related bioactivities, including cytotoxicity, mutagenicity, immunosupression, central muscle relaxant properties, anticonvulsive effects, monoamino oxidase inhibition, and direct vasidilator and blood pressure lowering activities have been observed. Examples of active compounds are **(174)**[144] and **(175)**.[143]

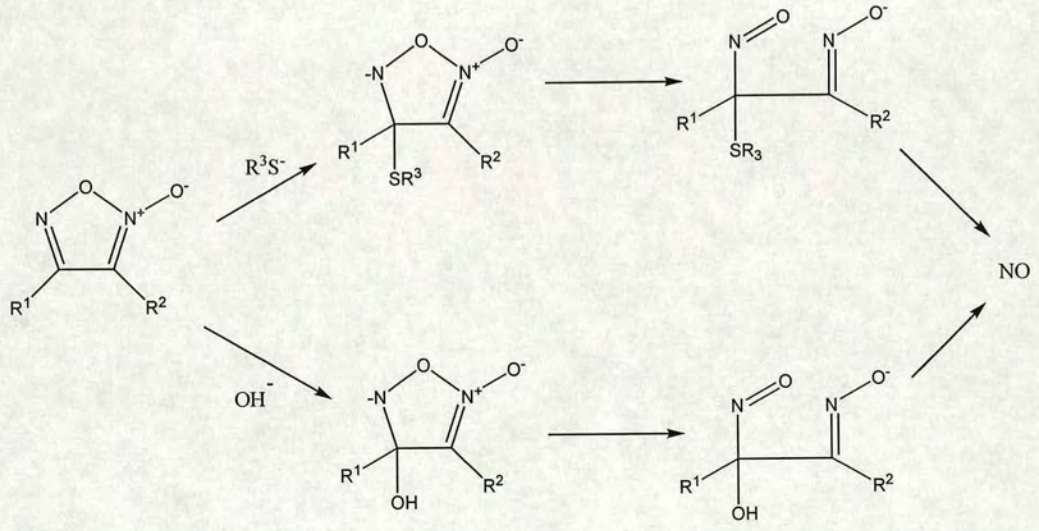


174



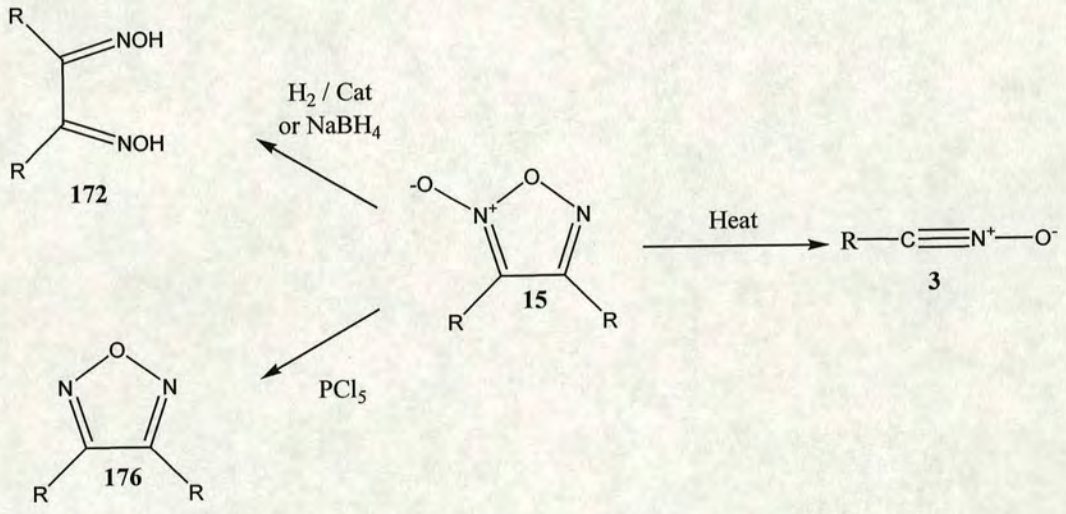
175

Several mechanisms for the release of NO have been postulated.[145] A common theme involves nucleophilic attack at the 3- and/or 4- position of the ring, either by thiols or a hydroxide, followed by furoxan ring opening and subsequent elimination of NO (Scheme 72).



Scheme 72

There is also interest in the transformations that the furoxan ring can undergo. Although generally stable to electrophiles and oxidising conditions, nucleophilic substitution reactions have been reported.[25] Moreover, the ring can undergo a retrocycloaddition at high temperatures, often greater than 200 °C, to afford nitrile oxides (**3**).[25] Hydrogenation of furoxans over a metal catalyst usually leads to 1,2-dioximes (**172**) as does treatment with sodium borohydride.[146] However, under more forcing conditions, e.g. Raney nickel as catalyst at elevated temperature or reduction with $LiAlH_4$, cleavage of the C-C bond can also occur giving amines.[146] Deoxygenation with reagents such as PCl_5[147] and $P(OEt)_3$[148] affords 1,2,5-oxadiazoles (furazans) (**176**) directly (Scheme 73).

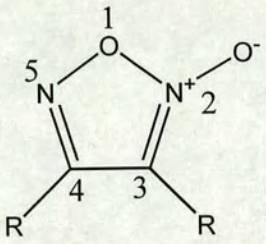


Scheme 73

2.8.1 Synthesis of 3,4-dipyranosyl-1,2,5-oxadiazole 2-oxides

The dimerisation of pyranosylnitrile oxides was chosen for the synthesis of dipyranosyl furoxans. The nitrile oxides were generated in the absence of dipolarophile from three precursors: pyranosylnitromethanes, pyranosyl aldoximes and pyranosyl hydroximoyl chlorides, as described previously (section 2.3).

Dehydration of pyranosylnitromethanes using a modified version of the Mukaiyama approach[9] was used to synthesise dipyranosyl furoxans (**177**) - (**180**). The results are summarised in Table 5.



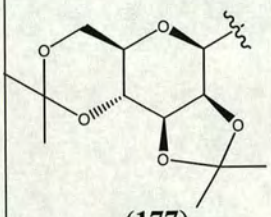
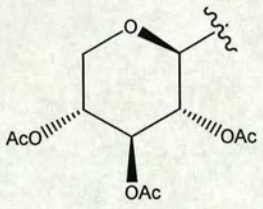
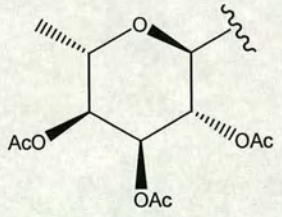
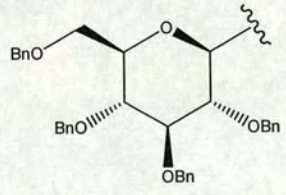
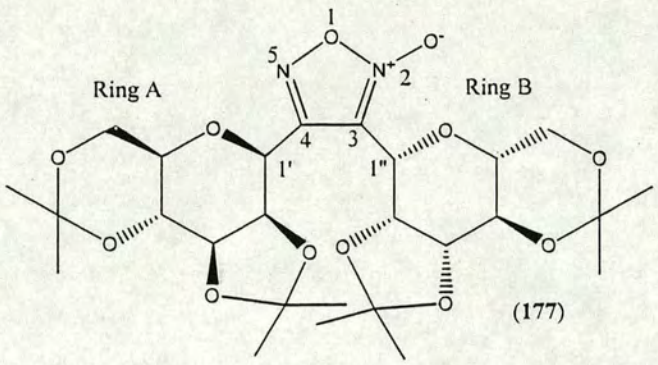
Furoxan R=	Yield / %	C-3, C-4 (ppm)	m/z (M-60)
 **(177)**	92	112.0, 153.1	571 (n/a)
 **(178)**	81	112.7, 153.7	603 (543)
 **(179)**	79	112.5, 153.8	631 (571)
 **(180)**	55	114.1, 154.9	1132 (n/a)

Table 5: Summary of results for furoxans **(177)** - **(180)**

3,4-Di(2,3:4,6-di-*O*-isopropyl-*β*-D-mannopyranosyl) furoxan (**177**) was obtained as white solid in 92% yield. The product was identified by ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum is of particular value in identifying the furoxan ring as there are diagnostic quaternary peaks at ca. 110 and 150 ppm corresponding to C-3 and C-4.[25] For compound (**177**) these peaks appeared at 112.0 and 153.1 ppm. The signals due to the pyranose ring protons between 61.5 and 75.8 'double up', consistent with the presence of two similar pyranose rings. This is also apparent in the methyl signals of the acetal protection. The 1,3-dioxane rings have peaks at 18.7, 18.7, 28.7 and 28.9 ppm due to the isopropylidene methyl groups as well as peaks at 99.9 and 100.0 ppm for the acetal carbons. There are corresponding peaks at 26.4, 27.3, 28.3 and 28.4 ppm and 110.4 and 110.5 ppm for the acetal carbons of the 1,3-dioxane rings.

The ^{1}H NMR spectrum is complicated due to the presence of two similar pyranose rings whose proton signals overlap at every position except the 1' and 1'' site where the two doublets corresponding to each anomeric proton are separated by 0.16 ppm. The small coupling constants seen for $J_{1'\text{-}2'}$ and $J_{1''\text{-}2''}$ of 2.5 Hz are consistent with the expected axial-equatorial relationship for these protons. Thus, the β-configuration of the nitromethylcompound (**130**) is retained in the furoxan product. To allow full analysis of the spectrum different solvents were tried but $CDCl_3$ gave the best resolution. Full assignment was achieved using 600 MHz COSY and 1D-TOCSY spectra. The 1D-TOCSY enables investigation of the two different ring systems (Figures 13, 14 and 15) enabling resolution of the overlapping signals. As with the parent pyranosylnitromethane, the presence of the 1,3-dioxalane and 1,3-dioxane rings fused onto the pyranose ring causes some distortion from the regular $^{4}C_{1}$ conformation as is shown by deviations in the coupling constants as compared to the tetra-*O*-acetyl case. A characteristic peak in the IR spectra of the compound was seen at 1606 cm^{-1} due to the C=N vibration.



600 MHz spectrum for (177)

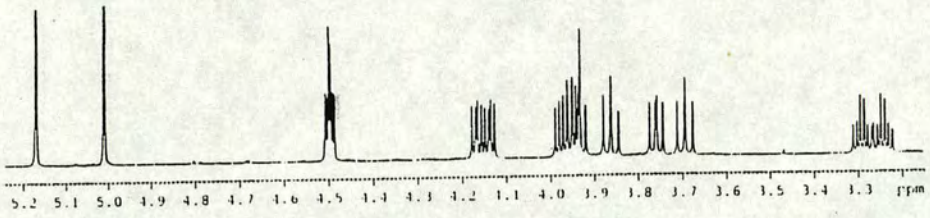


Figure 14

1D TOCSY for Ring A

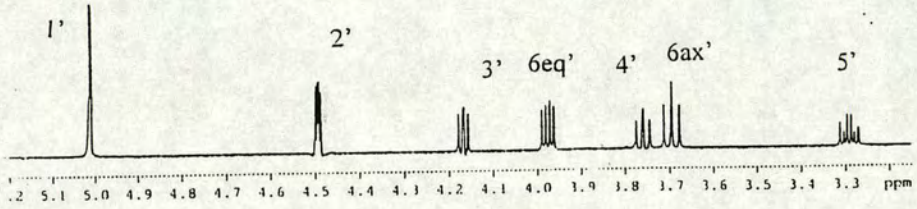


Figure 15

1D TOCSY for Ring B

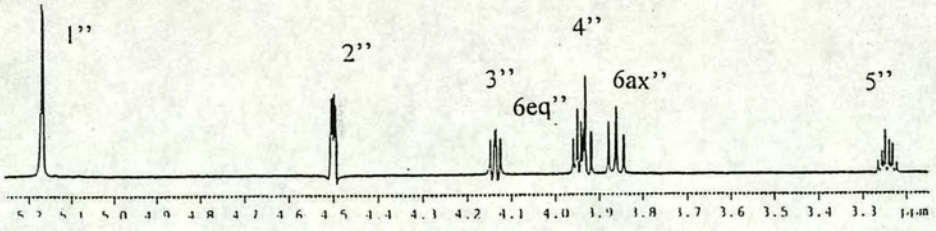
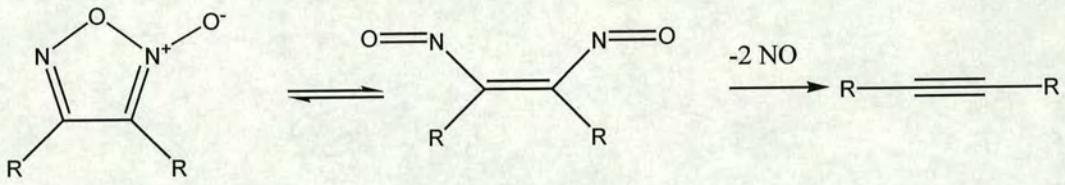


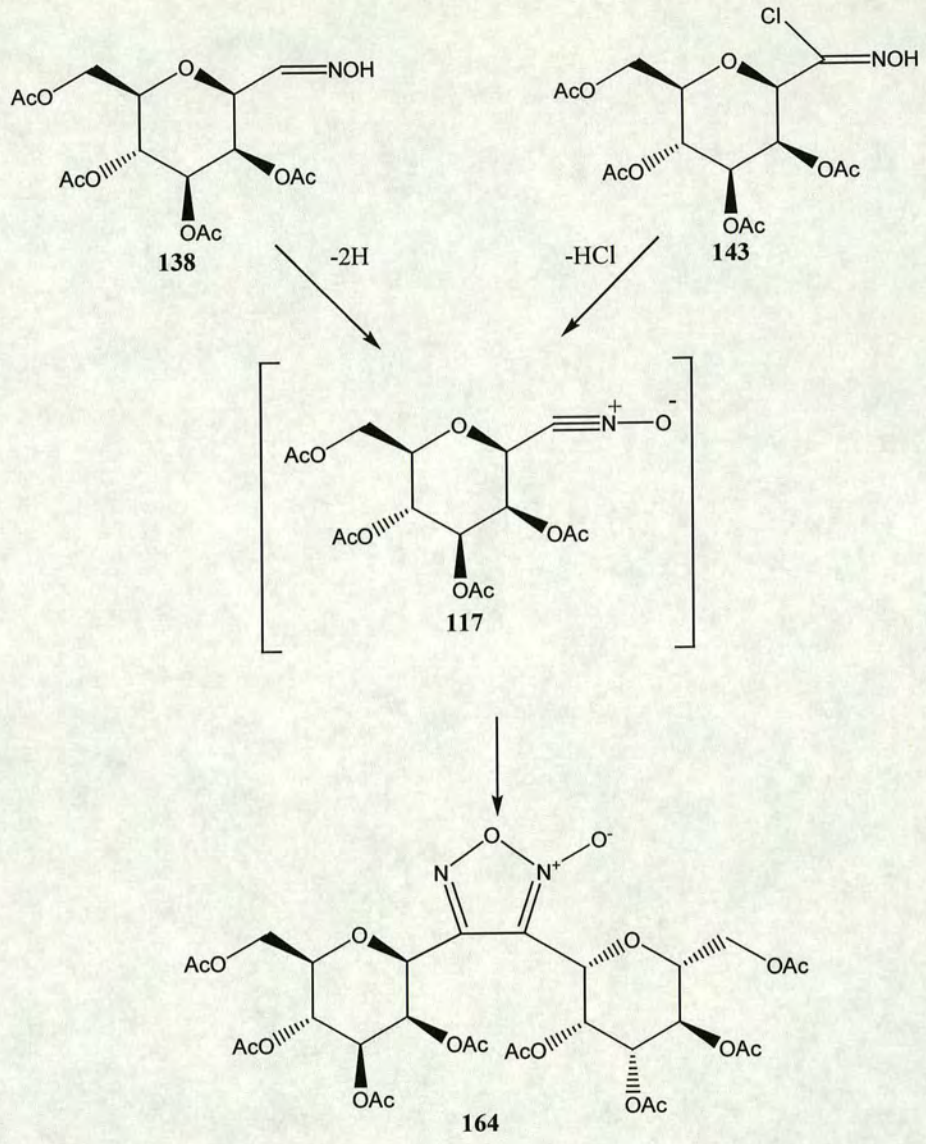
Figure 16

A common feature of the mass spectrum of furoxans is a prominent fragment peak at M-60,[25] which is attributed to the collapse of the heterocycle to an alkyne with the expulsion of N_2O_2 (Scheme 74). This peak is in evidence for most of the dipyranosyl furoxans with the exception of (**174**) where other fragmentation paths dominate. The M-16 peak due to the loss of oxygen, which is usually present for heterocyclic *N*-oxides, is weak for dipyranosyl furoxans.



Scheme 74

To establish the most efficient route to dipyranosyl furoxans, generation of 3,4,5,6-tetra-*O*-acetyl-β-D-mannopyranosyl furoxan (**164**) from the mannopyranosyl oxime (**138**) and mannopyranosyl hydroximoyl chloride (**143**) with subsequent dimerisation was attempted using the conditions described previously involving sodium hypochlorite oxidation and base-catalysed dehydrohalogenation respectively (Scheme 75).



Scheme 75

Using aldoxime (**138**) as precursor yielded furoxan (**164**) in 32% yield. Due to the low yield of the reaction it was apparent that this route had no advantage over the Mukaiyama approach, described earlier. With the hydroximoyl chloride (**143**) as precursor, furoxan (**164**) was obtained in 99% yield.

The ^{13}C spectrum shows the diagnostic peaks at 110.5 and 152.7 ppm due to C-3 and C-4 of the furoxan ring as well as the expected resonances attributable to the two peracetylpyranosyl rings. The ^{1}H spectrum is again complicated by the overlapping signals of the two pyranose rings. However, the 1'-H and 1''-H protons are well resolved ($\Delta\delta$ 0.24

ppm) and allowed $J_{1'-2'}$ and $J_{1''-2''}$ values of 1.0 Hz to be determined which are consistent with the axial-equatorial configuration for these protons. The mass spectrum shows the characteristic M+1 parent ion peak at 747 amu as well as the diagnostic M-60 breakdown peak at 687 amu. The IR has two distinguishing vibrations at 1743 cm^{-1} due to C=O of the acetate protection and at 1606 cm^{-1} due to the C=N of the furoxan ring.

The structure of furoxan (**164**) was confirmed by X-ray crystallography. (Figure 16). A noteworthy feature of the crystal structure is disorder in the furoxan moiety, with the N-oxide substituent being located at the 2- and 5-positions in a ratio of 85:15. Disorder of this type[149, 150] has been reported previously for diphenyl- and tetramethylene-furoxans and some norbornane-fused furoxans.[151] Selected bond lengths, bond angles and torsion angles for the furoxan ring system are shown in Table 6.

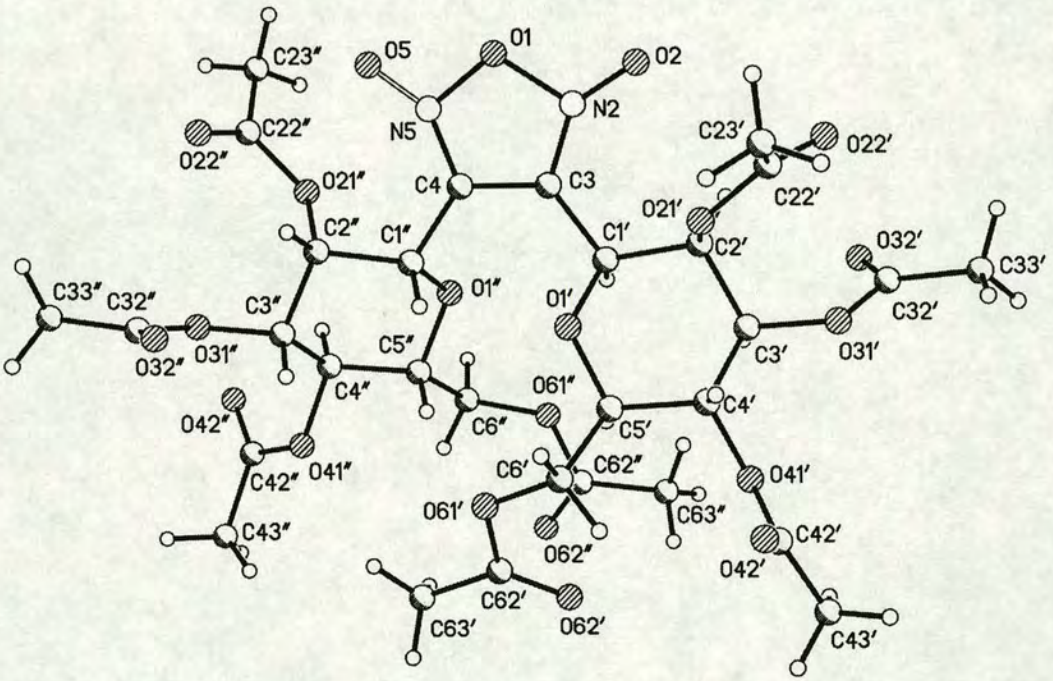
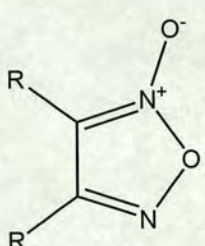


Figure 16

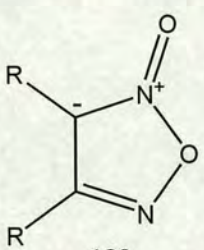
Bond lengths / Å	Bond Angles / °	Torsion angles / °
O(1)-N(2) 1.465(7)	O(1)-N(2)-C(3) 105.1(5)	O(1)-N(2)-C(3)-C(4) 0.16
N(2)-C(3) 1.319(8)	N(2)-C(3)-C(4) 108.3(5)	N(2)-C(3)-C(4)-N(5) 0.29
C(3)-C(4) 1.418(9)	C(3)-C(4)-N(5) 110.6(5)	C(3)-C(4)-N(5)-O(1) -0.68
C(4)-N(5) 1.309(7)	C(4)-N(5)-O(1) 107.3(5)	C(4)-N(5)-O(1)-N(2) 0.76
N(5)-O(1) 1.355(8)	N(5)-O(1)-N(2) 108.7(4)	N(5)-O(1)-N(2)-C(3) -0.57
N(2)-O(2) 1.180(7)	O(1)-N(2)-O(2) 111.2(5)	O(1)-N(2)-C(3)-C(1') 177.51
	C(3)-N(2)-O(2) 139.7(6)	O(2)-N(2)-C(3)-C(1') -1.19
		O(1)-N(5)-C(4)-C(1'') -179.63

Table 6: Selected bond angles, lengths and torsion angles for (**164**)

The atoms of the furoxan unit O(1), N(2), C(3), C(4), N(5), O(2) are near planar (maximum deviation 0.004 Å), as are the atoms of C(1'), C(3), C(4), C(1'') linking the oxadiazole to the two pyranoid substituents. The bond lengths are typical of furoxans[25] and indicate π-electron delocalisation over all six atoms with the exocyclic oxygen attached to N(2) causing significant distortion of the oxadiazole ring. Of particular note is the long O(1)-N(2) and short N(2)-O(2) bonds. C(3)-C(4) is also shortened corresponding to partial double bond character and N(2)-C(3) is longer than C(4)-N(5), consistent with contributions of (**181**) – (**184**) to the resonance hybrid. The bond angles of the C=NO_2 unit are also typical of 3,4-disubstituted furoxans, with O(2)-N(2)-C(3) significantly larger than O(2)-N(2)-O(1) [139.7 ° *cf* 115.2°].



181



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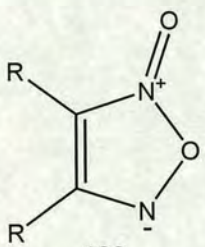

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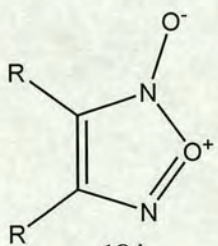

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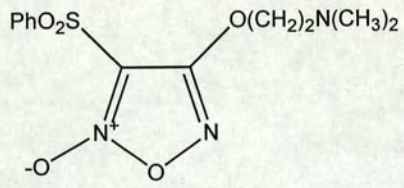
2.8.2 Summary and future work

The generation of pyranosyl nitrile oxides and their dimerisation to the furoxans by both dehydration of pyranosyl nitromethanes and dehydrohalogenation of pyranosyl hydroximoyl chlorides occur in good to excellent yields. The use of pyranosyl aldoximes as precursors was less efficient. As the route involving pyranosyl nitromethanes requires two less steps it is the method of choice, although the pyranosyl hydroximoyl chloride approach takes less time.

A desirable feature for furoxans as NO generators is water solubility, as this enables their study under physiological conditions. This has been reported for furoxans with side chains containing amine groups (e.g. **185**).[144] It is envisaged that water-soluble furoxans could also be obtained *via* deacetylation of the dipyranosyl 1,2,5-oxadiaxole 2-oxides.[123]



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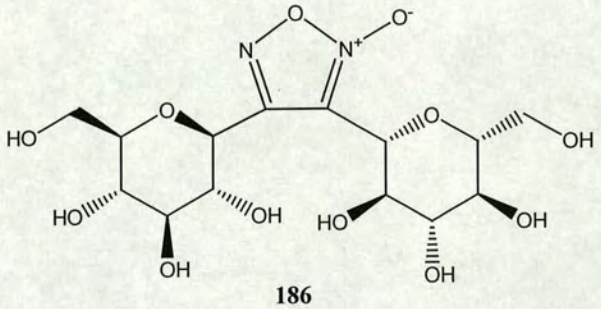
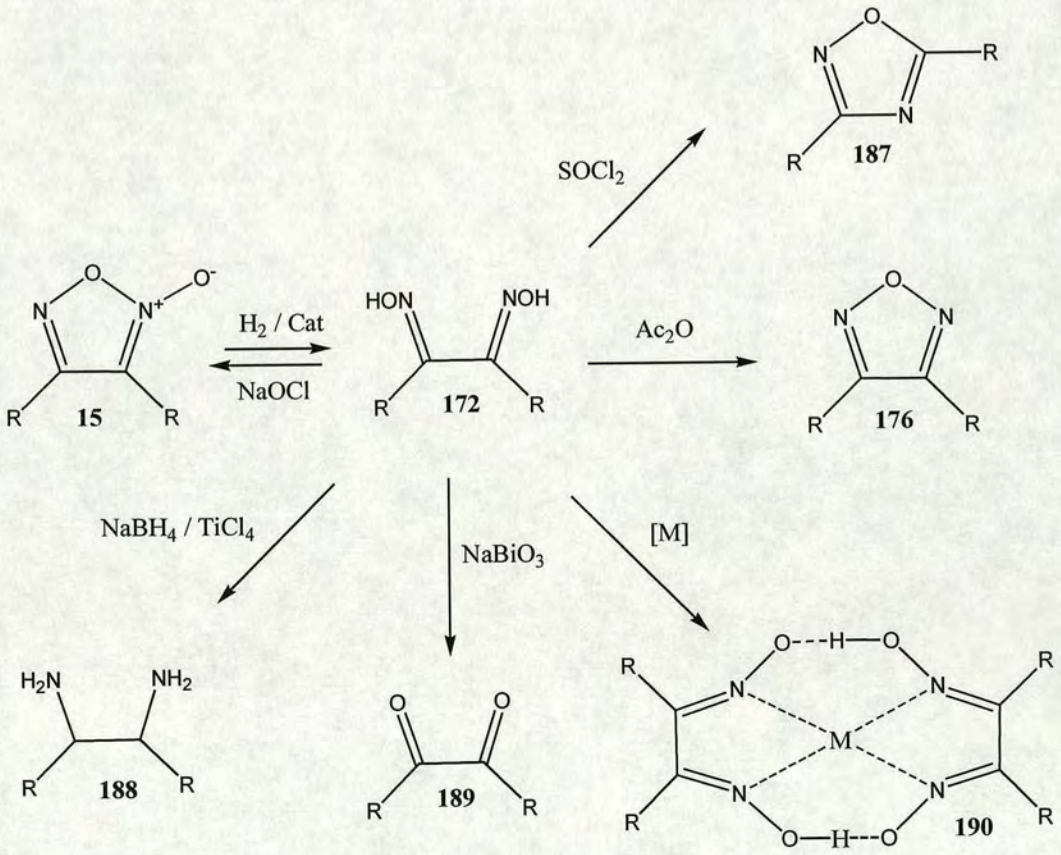


186

2.9 Ring opening reactions of furoxans.

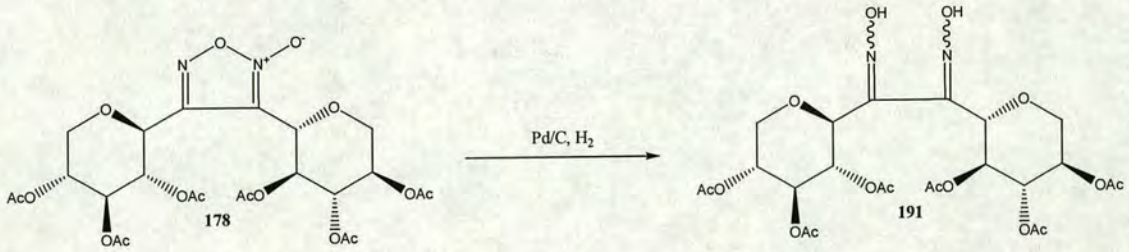
The relatively easy access to dipyranosyl furoxans prompted us to investigate their chemistry. The chemistry of furoxans is varied and there are a number of reviews in the literature.[25] An interesting reaction is the reduction of furoxans to 1,2-dioximes (**172**) often termed glyoximes. These compounds have been reported to give access to a number of derivatives (Scheme 76), for example they can be converted to the furazan (**176**) by treatment with reagents such acetic anhydride[152] and silica gel,[153] or undergo a Beckmann rearrangement to give 1,2,4-oxadiazole (**187**).[154] Conversion of glyoximes to diamines (**188**), using such reagents as sodium borohydride[155] and to 1,2-diketone (**189**), utilising reagents such as $NaBiO_3$[156] have also been documented. Another interesting property of dioximes is there ability to complex metals (**190**). For example, the concentration of nickel may be determined by reaction with dimethylglyoxime.



Scheme 76

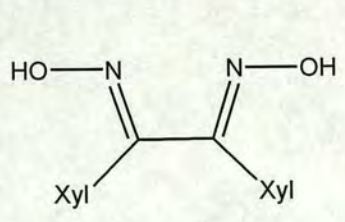
With this in mind attempts were made to synthesise dipyranosylglyoximes. Two furoxans were chosen for study. Firstly, 3,4-di(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl) furoxan (**178**) as this could be synthesised most readily from the parent aldose. Secondly, 3,4-di(2,3:4,6-di-*O*-isopropyl-*β*-D-mannopyranosyl) furoxan (**177**) due to its stability towards nucleophiles. A search of the literature showed that there are two main methods for the reduction of furoxans to glyoximes: catalytic hydrogenation and reduction with complex hydrides, e.g. sodium borohydride.[146]

The first approach considered was hydrogenation using Pd/C as catalyst (Scheme 77). Treatment of furoxan (**178**) with hydrogen in the presence of the catalyst gave two products: a white solid (53%) and an unidentified baseline material. The solid was identified by ^{1}H and ^{13}C NMR spectroscopy along with mass spectrometry as the dipyranosylglyoxime (**191**) as a mixture of geometric isomers.

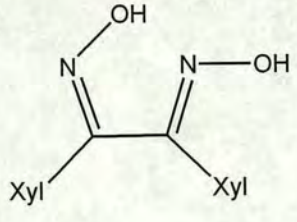


Scheme 77

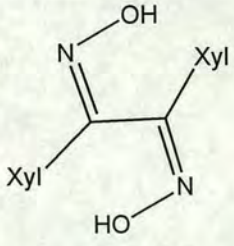
The three possible isomers (*Z,Z*), (*E,Z*) and (*E,E*) are shown below. The appearance of three peaks in the region assigned to the C=NO signal, between 145 and 150 ppm, is evidence for the presence of more than on isomer. It is likely that one isomer is a either the *E/E* or Z/Z isomer, which contain a rotational symmetry axis and thus should only have one C=NOH peak in the ^{13}C NMR spectrum, whilst the other is the *E/Z* arrangement giving two peaks for the C=NOH. It is possible that the baseline material could be an amine formed by over-reduction of the oxime, although there is no evidence for this.



191(*Z,Z*)



191(*E,Z*)



191(*E,E*)

In hope of obtaining the glyoxime as a single isomer, Raney nickel was used as catalyst. Hydrogenation of furoxan (**178**) using the Raney nickel catalyst gave a red oil, whose TLC showed two products, one baseline material and one less polar spot. These were separated by chromatography to give a white solid (77%) and a red oil. The white solid was identified as a single isomer of dioxime (**191**). The compound was characterised by ^{13}C and ^{1}H NMR spectroscopy. The presence of only one isomer was evident in the ^{13}C NMR spectrum, which contains two quaternary peaks at 146.0 and 148.6 ppm that are characteristic of dioxime signals.[157] The presence of two C=NOH peaks indicates an *E/Z* arrangement as this has no rotational axis of symmetry. The ^{1}H NMR spectrum, like that of the parent furoxan, is complicated by overlapping of signals due to the two similar pyranose rings. There are two broad singlets at 9.73 and 9.92 ppm which are due to the NOH peaks, whilst the rest of the signals correspond to the pyranose ring protons and the protecting groups. Full assignment was obtained using 600 MHz NMR (Figure 17). An interesting feature is the large separation, 0.74 ppm, between the anomeric proton signals.

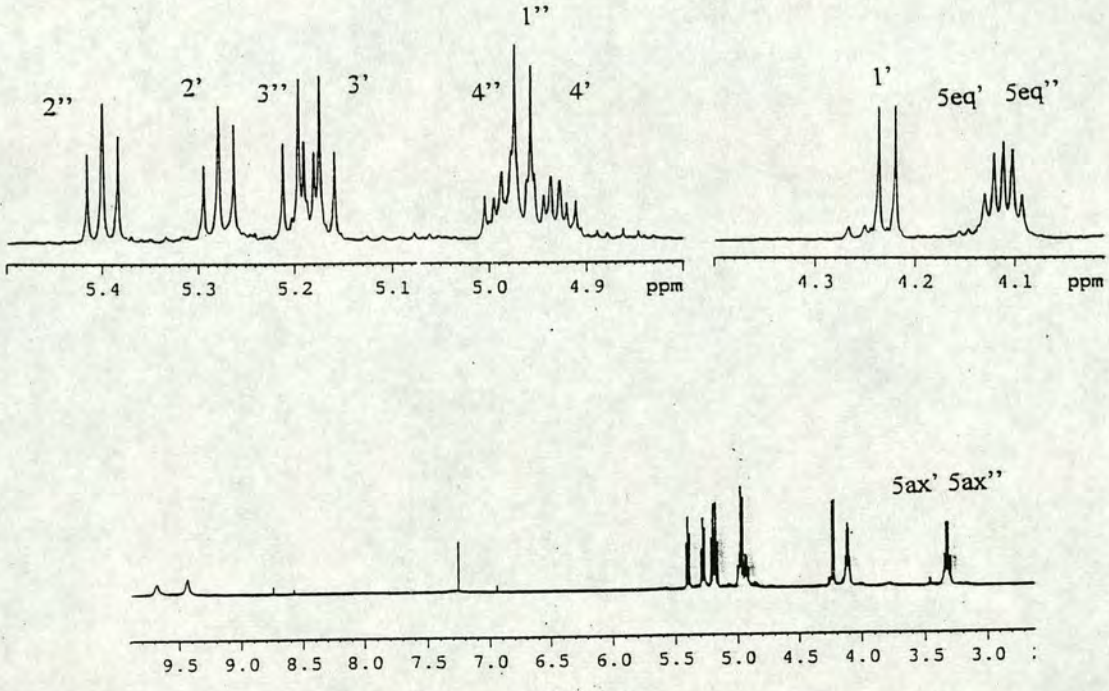
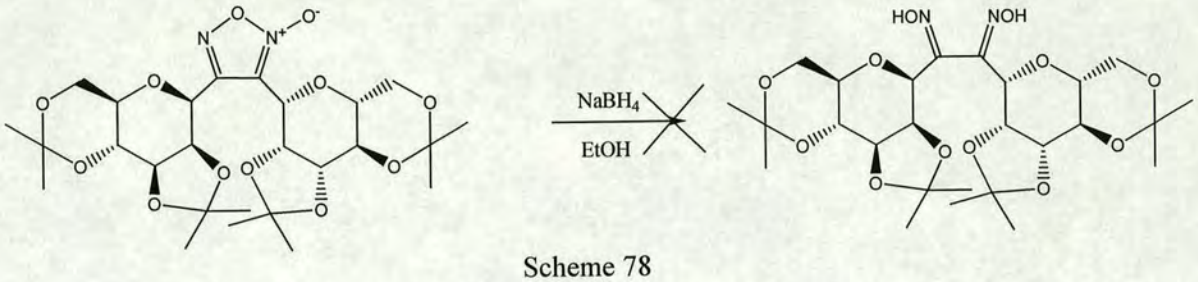


Figure 17

The second method of furoxan ring opening involved treatment with sodium borohydride (Scheme 78). It was envisaged that this would not be compatible with acetate protection, so its use was investigated on 3,4-di(2,3:4,6-di-*O*-isopropyl-*β*-D-mannopyranosyl) furoxan

(**177**). A solution of the furoxan in ethanol and sodium borohydride was heated to reflux for 24 hours and from the reaction mixture an oil was obtained. Although the ^{1}H NMR spectrum showed that no starting material remained there was no evidence of dioxime formation.



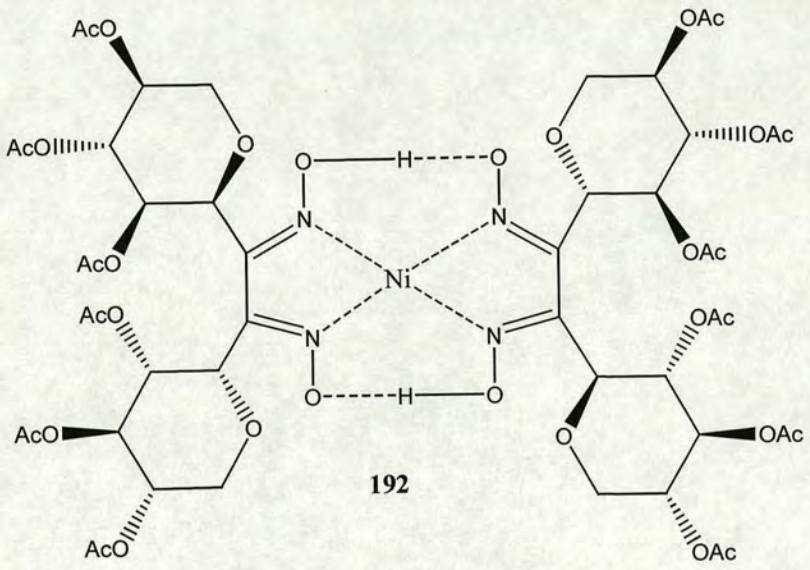
Scheme 78

2.9.1 Reactions of dipyranosylglyoximes

2.9.1.1 Chelation to metals.

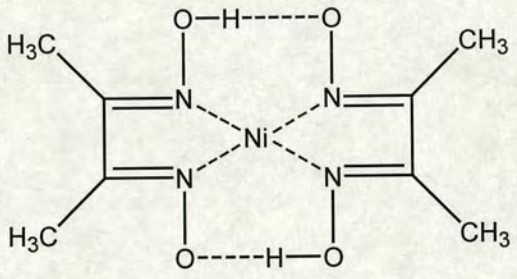
Asymmetric synthesis is one of the most challenging aspects of synthetic chemistry. There are a number of adopted strategies including the use of chiral catalysts, for example Sharpless epoxidation.[158] By introducing chirality into the catalyst system an influence on the stereochemistry of the catalysed reaction can be inferred. Examples of dioxime complexes were known in the literature[159] and so attempts to chelate the dipyranosyl dioximes with a metal, in this case nickel, were undertaken.

Treatment of 3,4-di(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl) glyoxime (**191**) with nickel(II) chloride was accompanied by a colour change from green to orange. From the reaction mixture was isolated an orange solid, which was assigned structure (**192**). The complex (**192**) was characterised by ^{1}H and ^{13}C NMR spectroscopy. Compared with the glyoxime the spectra were simplified by the axis of rotational symmetry. Thus, all pyranose units are equivalent and only one set of signals appear in the spectra. In the ^{1}H spectrum only one doublet due to the anomeric position was apparent whilst in the ^{13}C spectrum a peak at 144.7 ppm, due to the C=NO was evident. This appears at slightly lower chemical shift than in the dioximes, possibly due to the effect of the metal.



192

This complexation of dipyranosylglyoxime (**191**) with nickel may explain the presence of the red oil during hydrogenation of furoxan (**178**) with Raney nickel. Spectroscopy data indicates that the red oil has the same structure as complex (**192**). It is concluded that the dioxime formed is reacting with nickel(II) impurities in the Raney nickel. Similar observations have previously been reported by Mukaiyama.[9] Whilst attempting the hydrogenation of dimethylfuroxan, using Raney nickel as catalyst, a red by-product was obtained which was identified as the nickel complex (**193**).



193

Unfortunately, as yet no crystal structure for the dioxime complex (**192**) has been obtained. However, a molecular model using the CACHE programme[160] has been created showing that complex adopts a slightly distorted square planar conformation (Figure 18). The model indicates that the metal centre should be accessible to substrates.

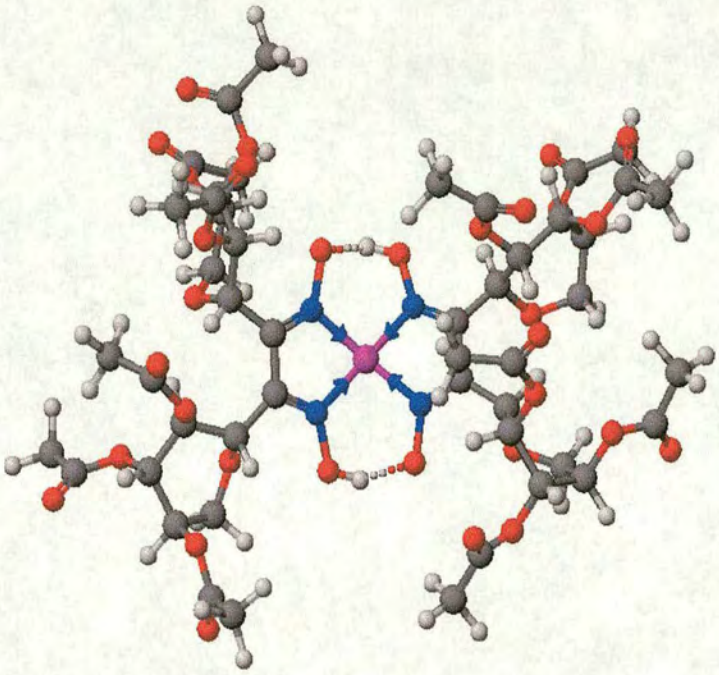
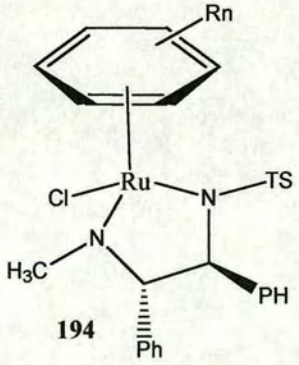
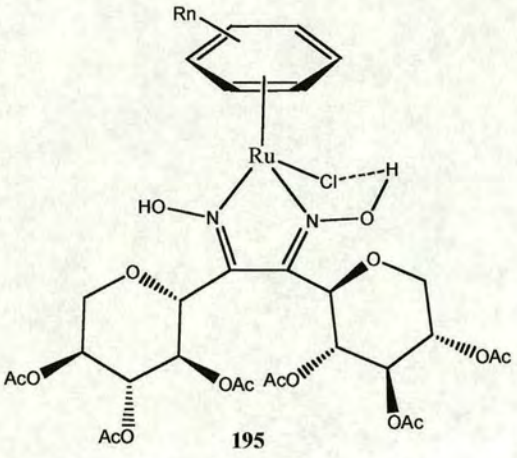


Figure 18

The complex (**194**) has been reported by Noyori[160] as a catalyst for the asymmetric reduction of ketones. It is envisaged that the dipyranosylglyoximes such as (**191**) may replace the diamine ligand and, due to potential hydrogen bonding, show useful selectivity. The molecular model for this potential glyoxime complex (**195**) is shown in Figure 19 and again indicates that the metal centre should be accessible to substrates.



194



195

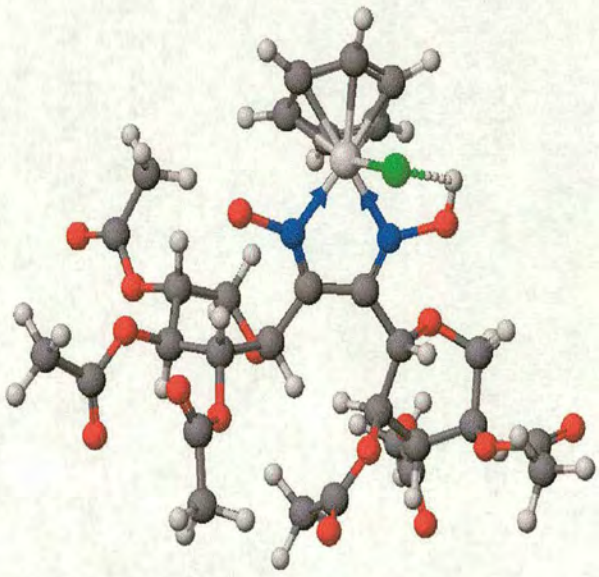
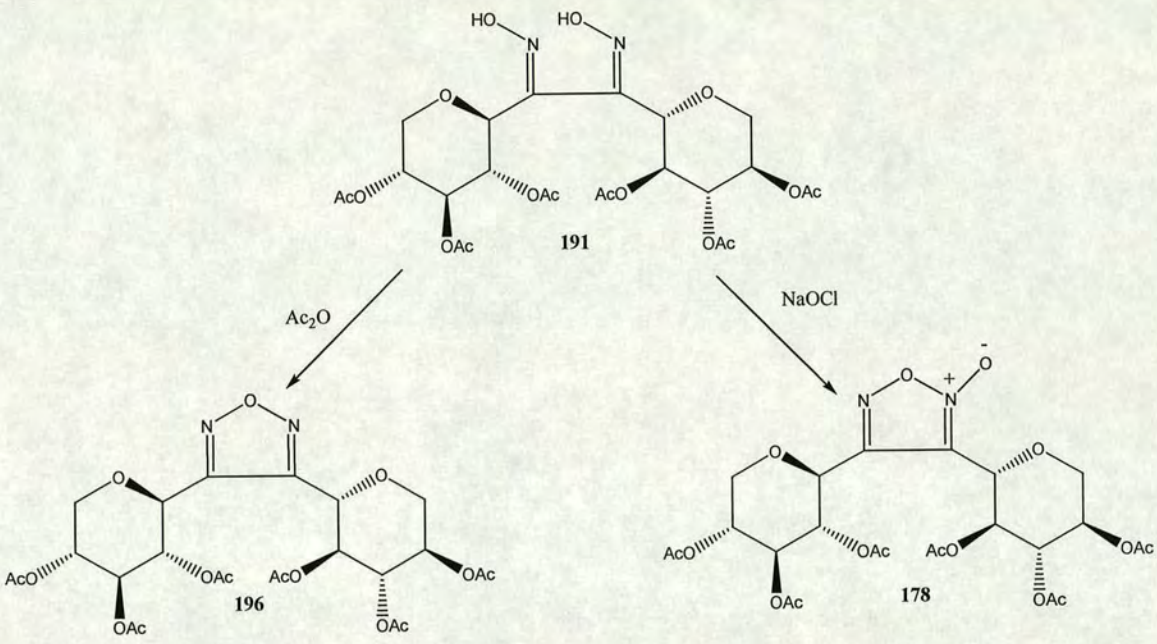


Figure 19

2.9.1.2 Ring forming reactions

Another feature of dioxime chemistry is the possibility of dehydration to furazan. Various reagents have been reported including acetic anhydride.[152] Treatment of 3,4-di(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-glyoxime (**191**) with acetic anhydride and DMAP gave an oil which was purified by chromatography top give a white solid whose structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy to be of furazan (**196**) (Scheme 79). As the furazan also has a rotational symmetry axis the NMR spectra are simplified. In the ^{1}H NMR there are the expected resonances for the peracetylated pyranose ring, with only one anomeric doublet, whilst in the ^{13}C NMR there is a quaternary signal at 150.9 ppm for C(3) and C(4) of the furazan ring.



Scheme 79

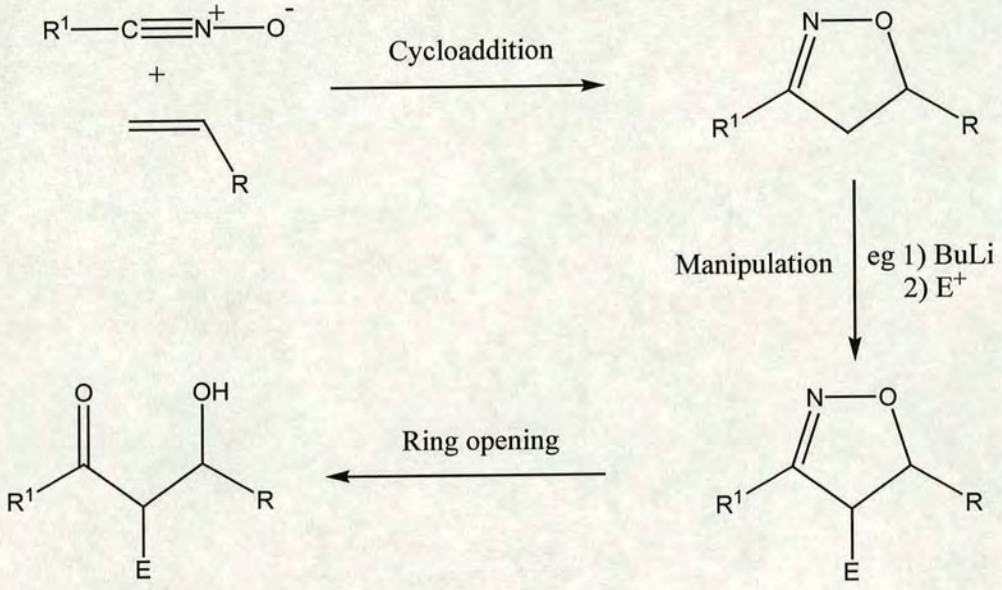
In order to confirm dioxime formation, attempts were made to convert glyoxime (**191**) to furoxan (**178**). The method chosen was a modified version of that of Boyer *et al*[162] using sodium hypochlorite as oxidant. The reaction yielded (**178**) in a 67% yield. The compound was characterised by ^{1}H and ^{13}C NMR by comparison with an authentic sample.

2.9.2 Summary and future work

Attempts to generate dipyranosyl glyoximes have proved successful and the synthetic utility of these compounds have been highlighted by conversion to furazan and complexation to nickel. The possibility of using the glyoxime in coordination chemistry is currently being investigated with the hope of synthesising asymmetric catalysts. The dioxime could also be converted to the diamine and the diketone as described previously and again used as chiral ligands.

2.10 Functionalisations of pyranosylisoxazolines

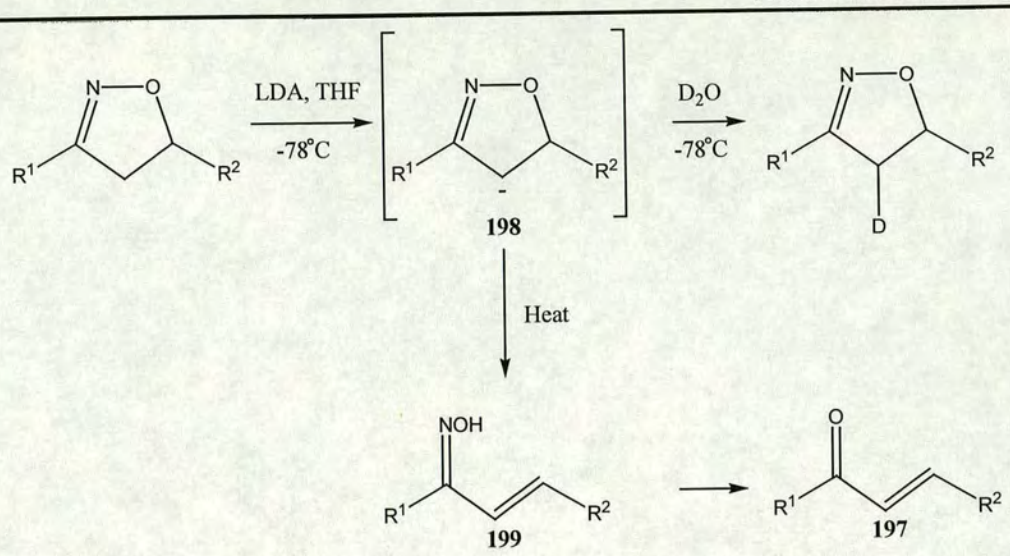
Having gained access to a variety of pyranosylisoxazolines, the next step in the nitrile oxide cycloaddition route is modification of the 4-position of the isoxazoline ring. This is one of the most attractive features of the nitrile oxide / isoxazoline approach as it greatly increases the variety of β-hydroxyketones and other products available (see section 1.2). The substitution is brought about by treatment with strong base followed by reaction with an electrophile (Scheme 80).



Scheme 80

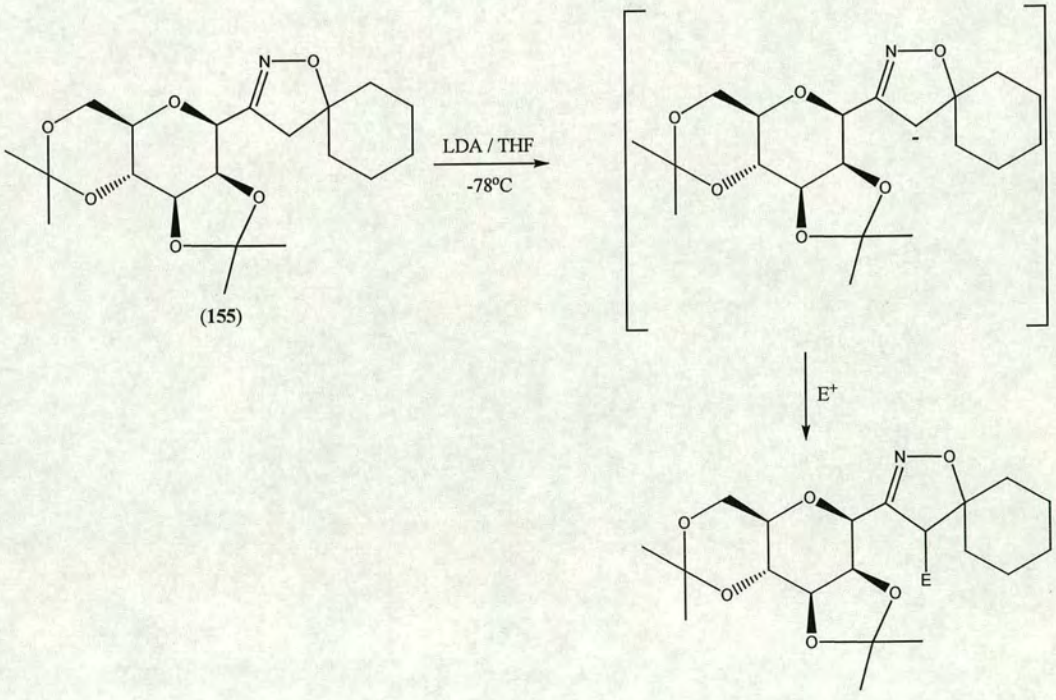
Jager *et al*[53] and several other groups have carried out a number of such substitutions leading to e.g. deuteration,[53] carboxylation,[53] silylation[53] and hydroxylation[46] of the isoxazoline ring. Of particular interest is the stereoselectivity of the reaction, whether the *cis* or *trans* product is obtained. This is often governed by the substituent at the 5-position.

Deprotonation at the 4-position of the isoxazoline ring can also provide an alternative route to α,β-unsaturated ketones (**197**) (Scheme 81). If the resulting anion (**198**) is allowed to warm to room temperature, rearrangement can take place leading to the α,β-unsaturated oxime (**199**), which can be converted to the α-enone (**197**) by treatment with e.g. titanium trichloride[163] and phosphorous pentachloride.[164]



Scheme 81

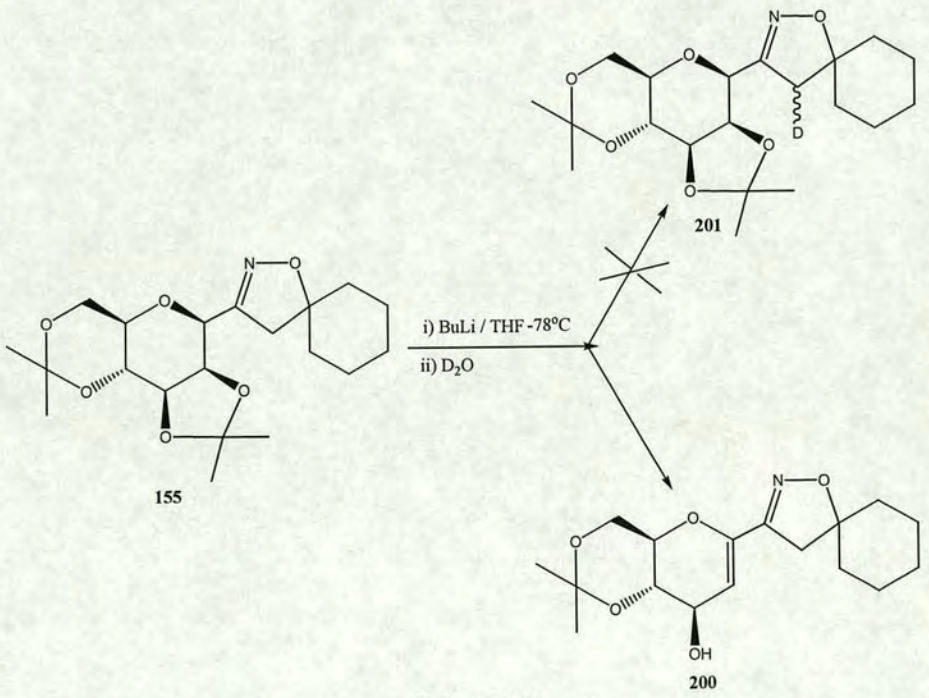
The pyranosyl isoxazoline (**155**) bearing a base-stable protecting group was considered to be a good candidate for attempted manipulation of the isoxazoline ring as outlined in Scheme 82.



Scheme 82

2.10.1 Attempted substitution reaction on 5-(spirocyclohexyl)-3-(2,3:4,6-di-O-isopropylidene-β-D-mannopyranosyl)-2-isoxazoline (155)

Addition of a solution of (**155**) in THF to butyllithium (or LDA) in THF at -78°C afforded a yellow solution, indicating anion formation. The solution was allowed to stir at -78°C for 2 hours and then D_2O was added. After warming to room temperature, excess butyllithium was quenched using aqueous ammonium chloride solution. Following the usual work up a white solid was obtained. The NMR of the compound indicated consumption of starting material but showed no sign of deuterium incorporation. There was evidence in the ^{13}C and ^{1}H spectra for the loss of one of the isopropylidene protecting groups (^{13}C : loss of peaks at 26.1 ppm, 28.2 ppm [$C(CH_3)_2$] and 109.8 ppm [$C(CH_3)_2$], ^{1}H : loss of peaks at 1.23 and 1.49 ppm). Other features of the ^{13}C spectrum included the appearance of a C-H peak at 106.7 ppm and a quaternary carbon at 145.8 ppm. The expected signals corresponding to the sugar protons H-1' and H-2' for compound (**201**), were not apparent. The most significant features in the proton spectrum were the appearance of a broad singlet at 2.4 ppm characteristic of an OH signal and a doublet at 5.07 ppm. In the mass spectrum there was a parent ion peak at 324 amu. The above evidence suggested the formation of the glycal (**200**) (Scheme 83).



Scheme 83

The formation of the glycal (**200**) rather than the substituted isoxazoline (**201**) explains several features of the NMR spectra, for example the loss of the signals for one isopropylidene group and the appearance of an OH peak in the ^{1}H spectrum. The structure of (**200**) accounts for the presence of the new quaternary carbon at 145.8 ppm corresponding to the anomeric position and a C-H at high chemical shift, 106.7 ppm, due to the olefinic carbon C(2). The conjugation of the isoxazoline C=N with the alkene unit explains the considerable shift in the signal assigned to the C=N (156.6 ppm to 151.6 ppm). The structure was confirmed X-ray crystallography (Figure 20).

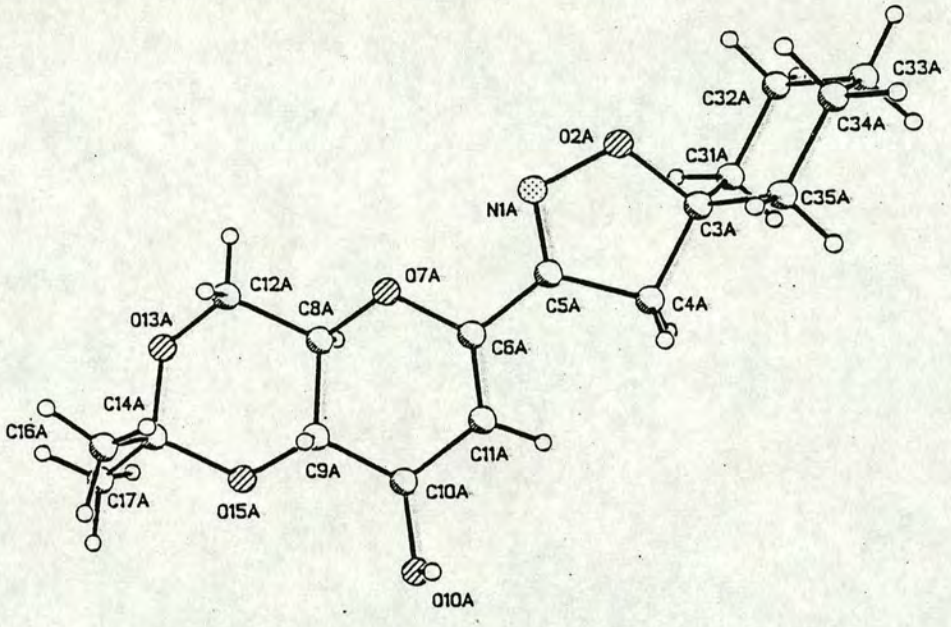


Figure 20

Introduction of unsaturation has a major impact on the shape of the pyranose ring, as evidenced by both the crystal structure data and the ^{3}J coupling constants for the ring protons. The crystal structure shows the shortening of the C(1)-C(2) bond from 1.526 Å in the pyranosyl aldoxime (**138**) to 1.329 Å indicating double bond character (Table 7). The bond angles of the ring protons show considerable flattening of the ring especially around O(1)-C(1)-C(2) and C(1)-C(2)-C(3). This flattening is further highlighted in the ^{1}H NMR where the coupling for $J_{2,3}$ is 2.4 Hz compared to a 5.2 Hz coupling seen in the parent isoxazoline (**155**).

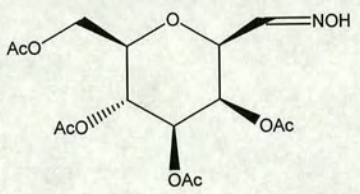
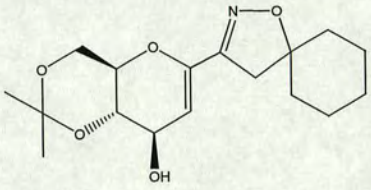
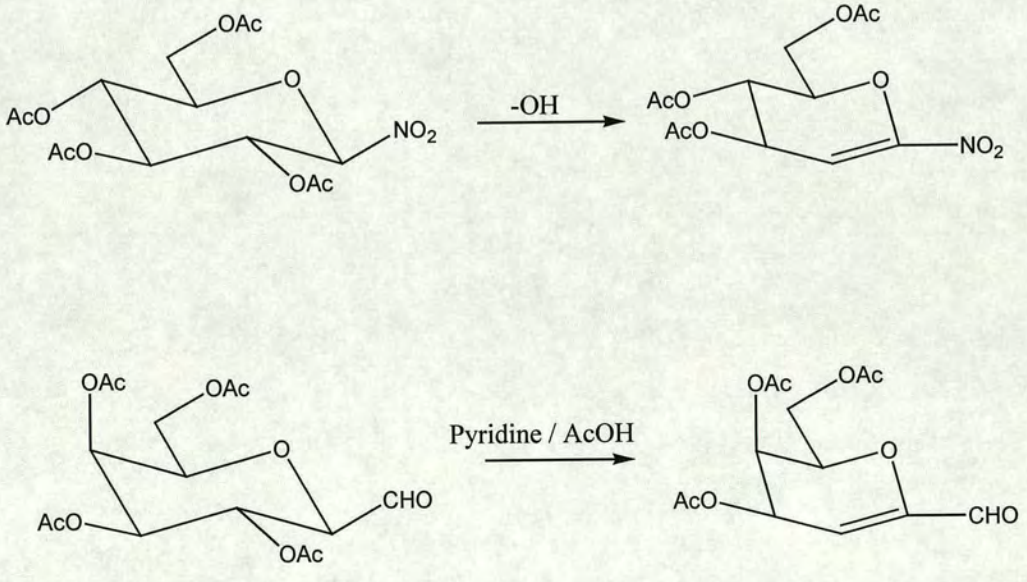
 **138**	 **200**
O(1)-C(1)-C(2) 110.3(4)	O(1)-C(1)-C(2) 123.80(14)
C(1)-C(2)-C(3) 110.5(4)	C(1)-C(2)-C(3) 123.90(15)
C(2)-C(3)-C(4) 108.6(4)	C(2)-C(3)-C(4) 107.67(13)
C(3)-C(4)-C(5) 109.5(4)	C(3)-C(4)-C(5) 109.06(13)
C(4)-C(5)-O(1) 109.5(4)	C(4)-C(5)-O(1) 110.05(13)

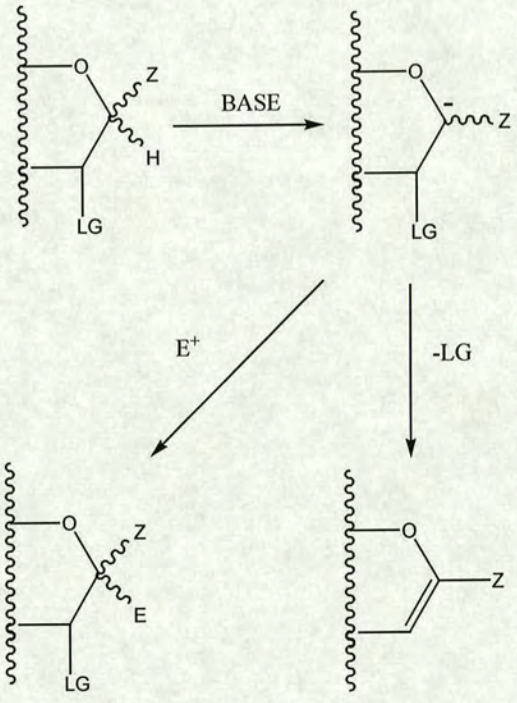
Table 7: Pyranose ring bond angles (°) for (**138**) and (**200**)

Glycal formation has been reported for a number of pyranosyl systems containing anion stabilising substituents at the anomeric position and good leaving groups at C(2) of the pyranose ring. Two examples are shown below (Scheme 84).[165, 166]



Scheme 84

Formation of the anomeric anion is possible for the pyranosylisoxazoline (**155**) due to the conjugatory stabilising effect of the isoxazoline ring. Once formed, the fate of the anion is determined greatly by the nature of the substituent in the 2-position and also the stability of the carbanion (Scheme 85).[167] The pyanosyl anion could act as a nucleophile and react with an electrophile. However, if the substituent in the β-position next to the anomeric centre is a good leaving group and the carbanion is relatively stable, then an elimination reaction can occur resulting in the formation of a glycal. Thus, glycal formation is seen when (**155**) is treated with base due to the stabilising nature of the isoxazoline ring and the relatively good leaving group. The final product is obtained by hydrolysis of the resulting hemiketal.



Scheme 85

There are two possible mechanisms for the elimination. The antiperiplanar nature of the anomeric proton and leaving group at the 2-position of the sugar ring mean that an E2 mechanism is possible (Figure 21), whilst the possibility of stabilising the anion by

conjugation into the isoxazoline ring also makes an E1cB mechanism feasible (Figure 22). The mechanism of the reaction will be discussed in more detail later.

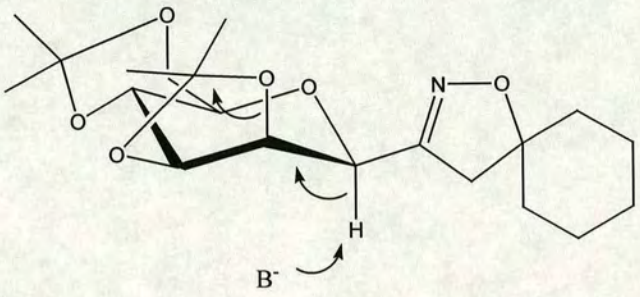


Figure 21

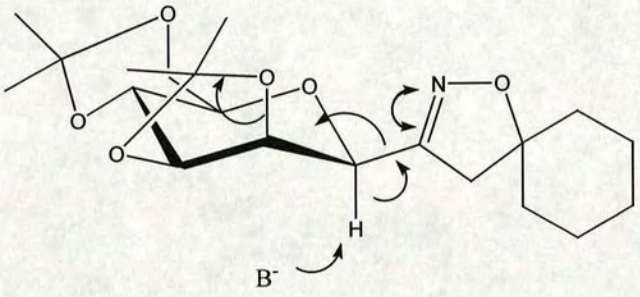
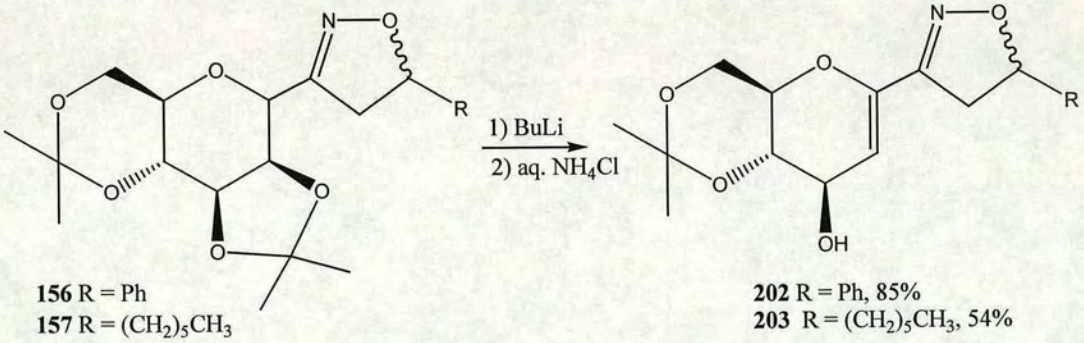


Figure 22

To investigate the scope of this reaction cycloadducts (**156**) and (**157**) were treated under similar conditions as for (**155**), and the products identified by ^{1}H and ^{13}C NMR spectroscopy. The results are summarised below (Scheme 86). The products were obtained in a similar diastereoisomer ratio as the starting materials.

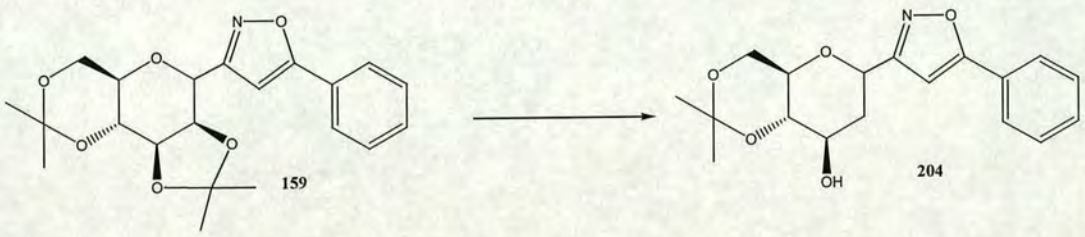


156 R = Ph
157 R = $(CH_2)_5CH_3$

202 R = Ph, 85%
203 R = $(CH_2)_5CH_3$, 54%

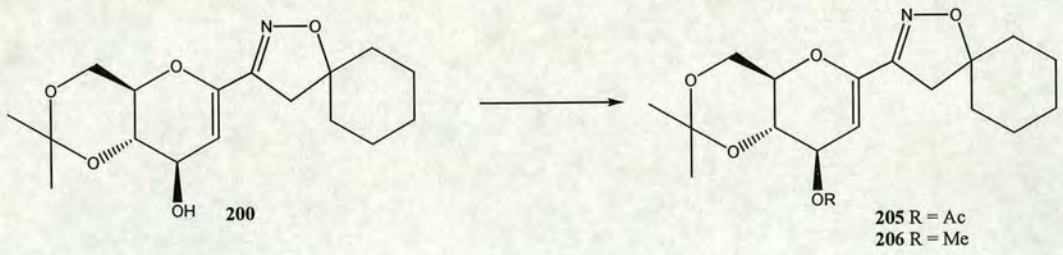
Scheme 86

Isoxazole (**159**) was reacted under similar conditions in order to ascertain whether 3-pyranosylisoxazoles behaved in the same manner as 3-pyranosylisoxazolines (Scheme 87). Following the usual work up the glycal isoxazole (**204**) was obtained in 89% yield and identified by ^{13}C and ^{1}H NMR spectroscopy, which again showed the characteristic carbon signals for the olefinic C-H for C-2' at 104.4 ppm, as well as a peak at 97.1 due to C-4 of the isoxazole ring and a quaternary signal at 144.1 ppm for the anomeric carbon. The ^{1}H spectrum had a doublet at 5.55 ppm due to the olefinic hydrogen at C-2 as well as a singlet at 6.53 for the proton of the isoxazole.



Scheme 87

Further support of the assigned structure was obtained by acetylation and methylation of the free hydroxyl group at the 3' position of the glycal (Scheme 88). Using standard acetylation conditions 5-(spirocyclohexyl)-3-(4,6-di-*O*-isopropylidene-3-*O*-acetyl-2-deoxy-D-mannopyranosyl)-2-isoxazoline (**205**) was obtained in 82 % yield. Its ^{1}H NMR was similar to that of the parent compound (**200**) except for an extra peak at 2.14 ppm due to the CH_3 of the acetate group and a displacement of 3'-H from 4.50 ppm to 5.45 ppm. The ^{13}C spectrum confirmed the introduction of acetate protection with peaks at 21.1 and 170.8 ppm.



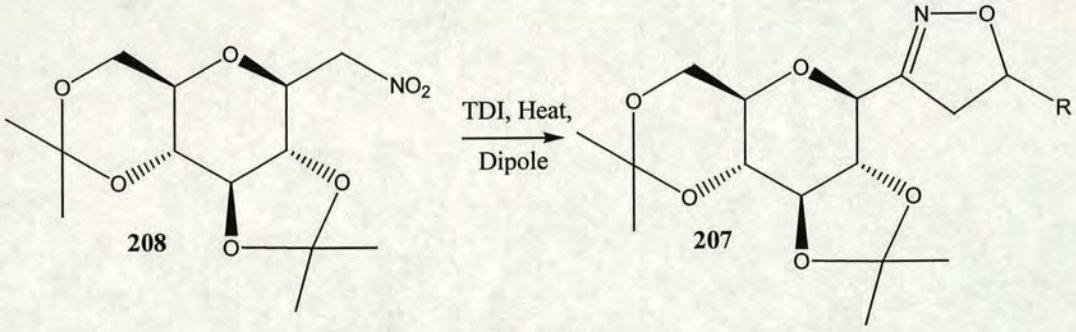
Scheme 88

Methylation of glycal (**200**) gave further support for the structure of the glycal. Methylation was achieved using potassium hydroxide and methyl iodide as described in section 2.10.2.1

below. The product (**206**) which was obtained in a 42% yield, showed a new signal at 3.50 ppm in the ^{1}H NMR attributable to the methoxy group.

2.10.2 Investigation of the effect of stereochemistry and leaving group on the elimination reaction

As described previously, there are two possible mechanisms for the elimination reaction, namely the E2 and E1cB. A prerequisite for an E2 elimination is an anti-periplanar relationship between the abstracted proton and leaving group. To establish which mechanism was taking place the elimination reaction was attempted on a pyranosylisoxazoline that did not possess this antiperiplanar relationship. A possible candidate would be an isoxazoline (**207**) derived from 3,4:5,7-di-O-isopropylidene-β-D-glucopyranosylnitromethane (**208**) (Scheme 89). Although this compound is described in the literature,[128] attempts to prepare it by acetonation of β-D-glucopyranosylnitromethane were unsuccessful. An alternative candidate, 5-(spirocyclohexyl)-3-(tri-O-methyl-β-D-xylopyranosyl)-2-isoxazoline (**209**) was therefore prepared (Scheme 90).



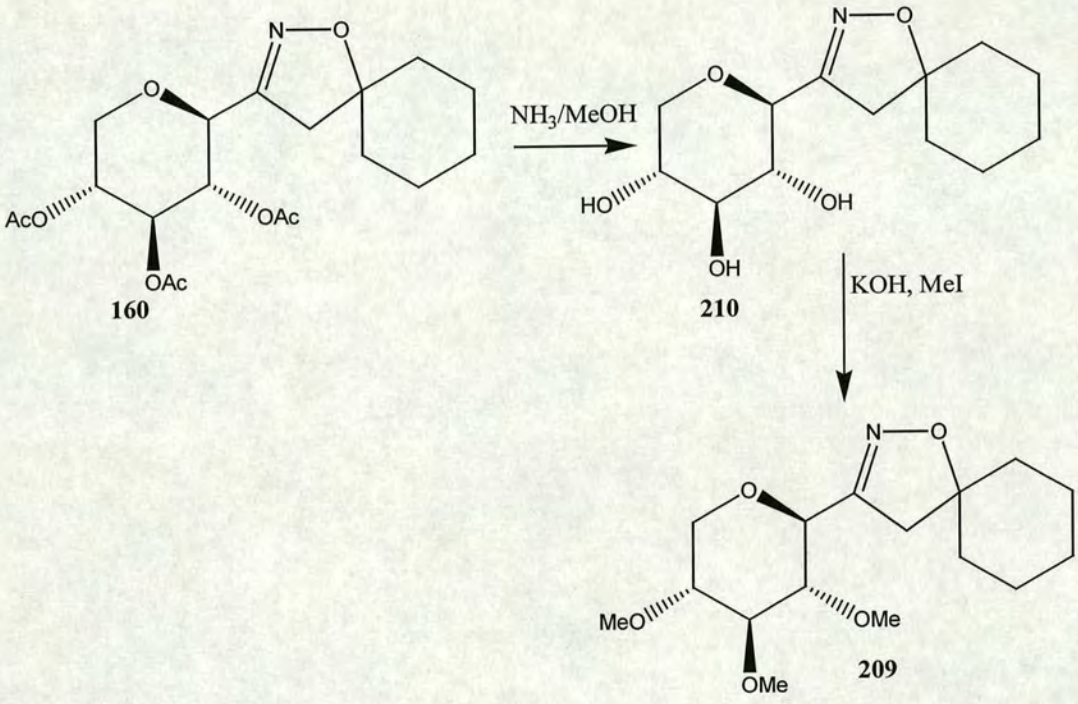
Scheme 89

2.10.2.1 Formation of 5-(spirocyclohexyl)-3-(tri-O-methyl-β-D-xylopyranosyl)-2-isoxazoline (209)

The first step in the synthesis of the tri-*O*-methyl isoxazoline (**209**) involved deacetylation of the triacetyl analogue (**160**) (Scheme 90). A number of conditions for deacetylation have been reported, including treatment with catalytic potassium cyanide[168] and sodium methoxide. The method selected for the present work involved the use of ammonia.[169] The

procedure simply involved treatment of the acetylated isoxazoline in methanol with ammonia, and removal of the solvent *in vacuo* to afford the isoxazoline (**210**), which was identified by NMR spectroscopy and mass spectrometry.

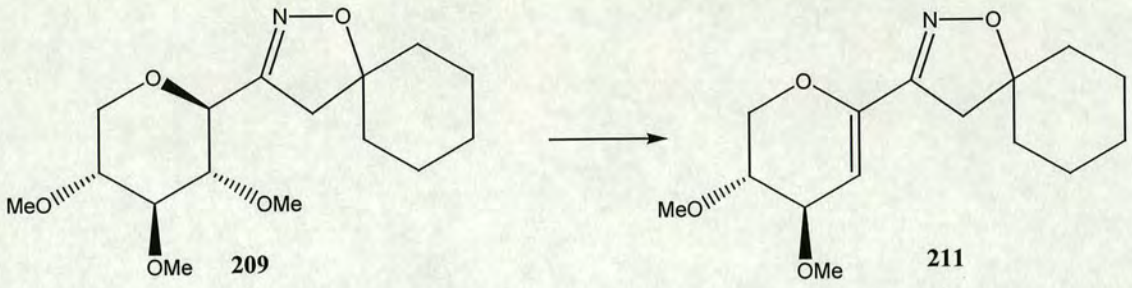
O-Methylation was achieved by treatment of isoxazoline (**210**) in DMSO with potassium hydroxide and methyl iodide. Following aqueous work up the protected isoxazoline (**209**) was obtained in 75% yield and characterised by NMR spectroscopy and mass spectrometry.



Scheme 90

2.10.2.2 Attempted glycal formation on 5-(spirocyclohexyl)-3-(tri-O-methyl-β-D-xylopyranosyl)-2-isoxazoline (209)

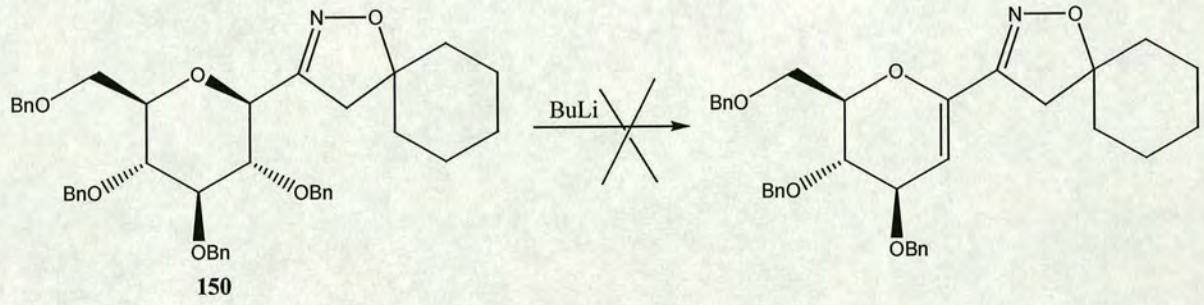
To investigate the mechanism of the elimination reaction, isoxazoline (**209**) was exposed to the usual elimination conditions (Scheme 91). An oil was obtained, which was purified by chromatography to give the glycal isoxazoline (**211**) in 40% yield, as well as some unreacted starting material (**209**) (28%).



Scheme 91

The reaction proved to be much slower than the previous examples. This could be due to a poorer leaving group and / or the change in stereochemistry at C(2). The lack of an antiperiplanar relationship between the leaving group and the anomeric proton suggests an E1cB mechanism rather than an E2. Similar effects have been reported for related systems.[167]

The corresponding reaction of 5-(spirocyclohexyl)-3-(2,3:4,6-tetra-O-benzy-β-D-glucopyranosyl)-2-isoxazoline (**150**) with butyllithium under the normal reaction conditions afforded only unreacted starting material (Scheme 92). This is a somewhat surprising result, as OBn is expected to be a better leaving group than OMe. A possible explanation is the steric demand of the benzyl ether, which may prevent access to the anomeric proton by the base. The use of a less bulky base such as methyllithium may overcome this steric barrier.



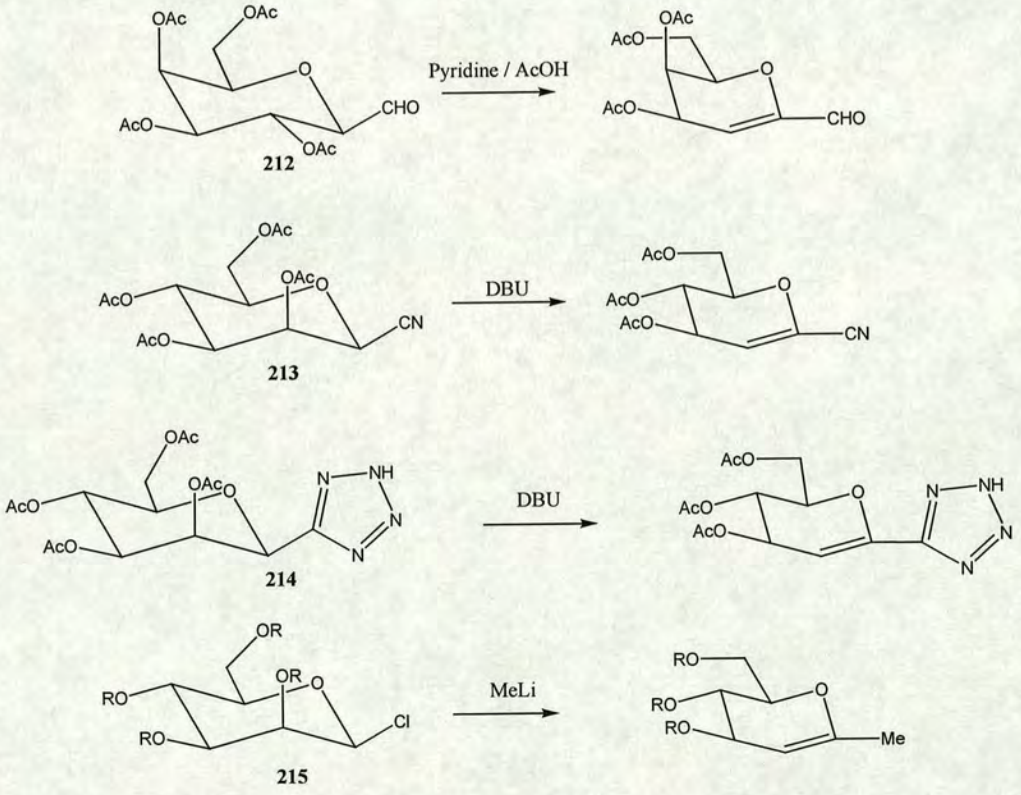
Scheme 92

2.10.3 Stability of the pyranosyl carbanion

The strength of base required to achieve anion formation is an indicator of the stability of the anomeric carbanion, the weaker the base the more stable the anion. Up to this point, the

reactions had been carried out using the very strong bases, butyllithium and LDA, which both have pK_{aH} values greater than 35. It was decided to investigate further the stabilising effect of the isoxazoline ring by testing the strength of base required to give glycal formation.

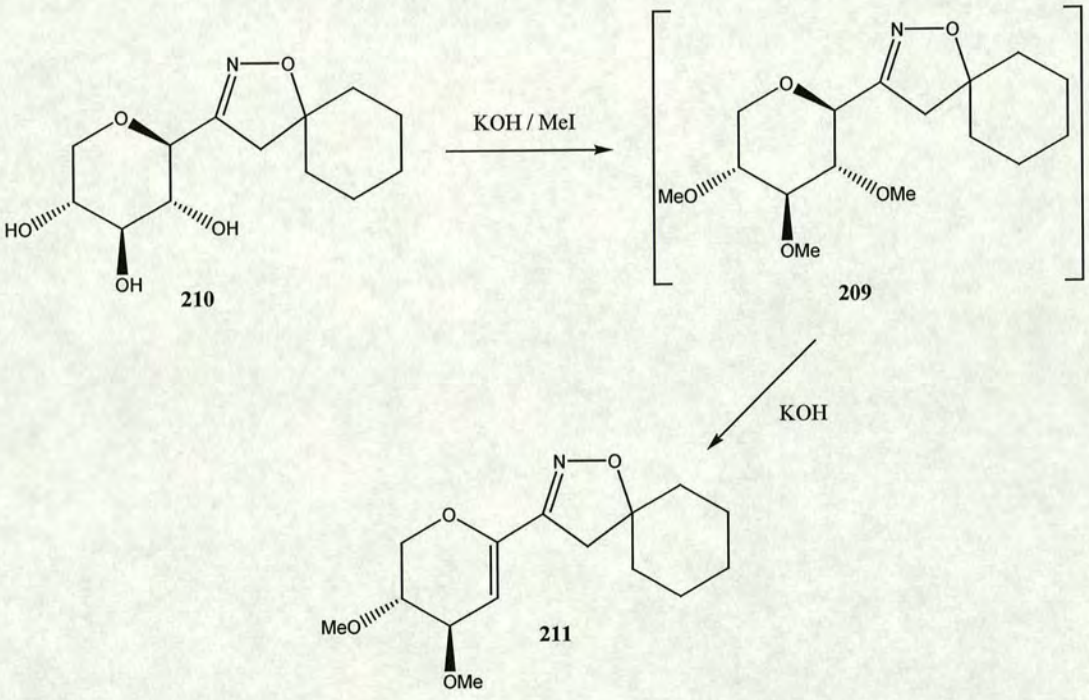
For *C*-pyranosyl aldehydes[166] (**212**) the stabilising effect of the formyl group is such that pyridine (pK_{aH} = 5.2) is a strong enough base (Scheme 93) whilst, for the *C*-pyranosyl nitrile[170] (**213**) the reduction in stabilisation is shown by the requirement of a stronger base, DBU (pK_{aH} ~ 12). This is also the case for the rare situation where a heterocyle, a tetrazole[170] (**214**), is attached to the anomeric position. If chlorine is used as the stabilising moiety (**215**) the lack of conjugatory stabilisation is highlighted by the requirement of methyllithium to achieve anion formation.[171]



Scheme 93

To test if the isoxazoline group provided similar stabilisation as the tetrazole, 5-(spirocyclohexyl)-3-(tetra-*O*-acetyl-β-D-xylopyranosyl)-2-isoxazoline (**153**) in dichloromethane was treated with DBU. Following work up a solid was obtained which was identified as starting material. There was no indication of glycal formation, thus indicating that the stabilising effect of the isoxazoline is less than that of the tetrazole.

However, the formation of glycal (**211**) during the attempted preparation of the tri-*O*-methyl isoxazoline (**209**) indicated that potassium hydroxide was a sufficiently strong base to give glycal formation. Whilst attempting methylation of isoxazoline (**210**) the reaction was left for a prolonged time yielding glycal (**211**) instead of the expected product (**209**) (Scheme 94). This observation led to the treatment of isoxazoline (**155**) with potassium hydroxide in DMSO. Following an overnight stir and an aqueous work up glycal (**200**) was obtained in 59 % yield (see Scheme 83). The pK_{aH} of potassium hydroxide is ~ 14. It is concluded that the pK_a of the anomeric proton must be in the range ~12 to ~14 pK_a as elimination occurs in the presence of potassium hydroxide but not DBU.

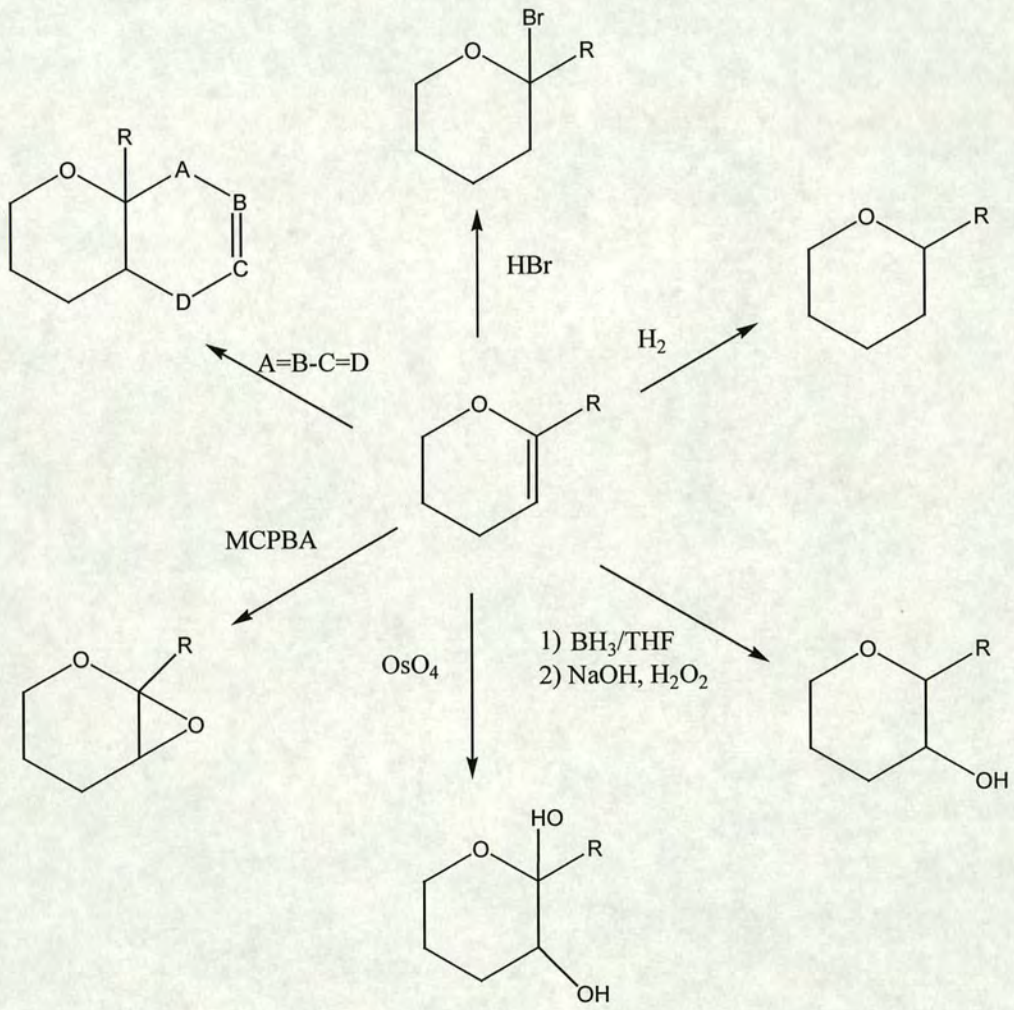


Scheme 94

From the results described above it can be concluded that treatment of pyranosylisoxazolines with base does not deprotonation in the isoxazoline ring, but rather causes an elimination reaction to afford glycal isoxazolines. Although an unexpected reaction, these glycals could be of synthetic interest (see following section).

2.11 Manipulation of the glycal isoxazolines

The formation of unsaturation in the pyranose ring provides a reactive site that can be chemically modified. Glycals are often utilised as building blocks in synthesis. Indeed, many routes to *C*-glycosides involve the use of glycals. Glycals readily undergo reactions such as bromination,[172] dihydroxylation,[110] epoxidation,[173] and hydroboration[110] (Scheme 95).

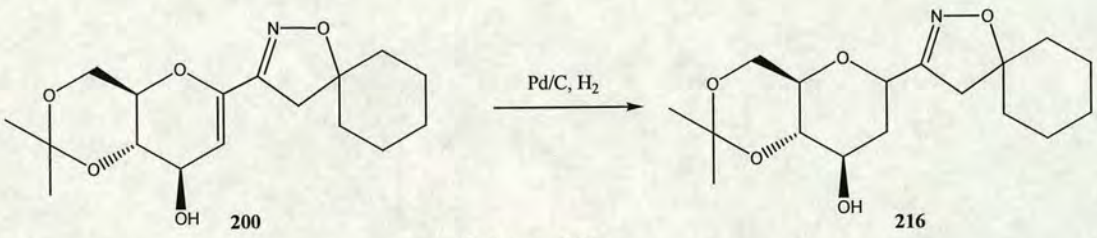


Scheme 95

Preliminary investigations of the addition of a range of electrophiles to the glycal were undertaken. A major consideration when attempting these reactions was whether the isoxazoline ring would be stable to the reaction conditions.

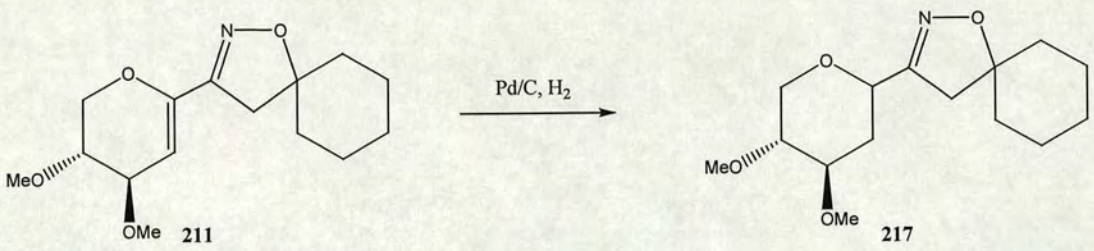
Hydrogenation of the glycal double bond was the first reaction attempted. To minimise potential cleavage of the isoxazoline ring, 5% Pd/C was used as catalyst as it was envisaged that hydrogenation of the olefinic bond would occur more rapidly than isoxazoline ring

opening. Glycal isoxazoline (**200**) in dry methanol was placed under an atmosphere of hydrogen in the presence of Pd/C and left to stir for 16 hrs (Scheme 96). Separation of the catalyst by filtration followed by removal of solvent in vacuo gave an oil containing two products, one a baseline material. From the mixture isoxazoline (**216**) was isolated in 62% yield by column chromatography. The baseline material was not characterised but gave a positive test with ninhydrin spray suggesting the formation of the γ-aminoalcohol due to ring opening of the isoxazoline. Characterisation of (**216**) was achieved using NMR spectroscopy. The ^{1}H NMR showed the disappearance of the doublet at 5.06 ppm due to the olefinic C-H and appearance of two new doublet of doublets of doublets signals at 1.75 and 2.23 ppm due to the new CH_2 group at the 2-position of the pyranose ring, the low chemical shift being indicative of the lack of an oxygen-based substituent. There was also a new signal at 4.37 ppm (doublet of doublets) due to the new proton at the anomeric position. The $J_{1,2a}$ coupling of 11.9 Hz suggests a diaxial arrangement and thus a β-configuration at the anomeric position. In the ^{13}C NMR the loss of a C-H peak at 106.7 ppm and a quaternary at 145.8 ppm indicate the absence of the double bond. This is confirmed by the appearance of a new CH signal at around 70 ppm and a CH_2 signal at 24.9 ppm due to the C-2' position. The low chemical shift of this peak again emphasises the lack of an oxygen-based substituent. Another interesting feature is the change in position of the C=N peak of the isoxazoline ring from 151.6 ppm to 157.2 ppm. This is consistent of the loss of conjugation with the imine group of the isoxazoline ring as previously described.



Scheme 96

The hydrogenation reaction was also successful for glycal (**211**) (Scheme 97). Subjecting (**211**) to the same hydrogenation conditions as described above gave (**217**) (56%), which was identified by NMR spectroscopy and mass spectrometry. A baseline material was also isolated which again gave a positive test with ninhydrin, suggesting γ-aminoalcohol formation



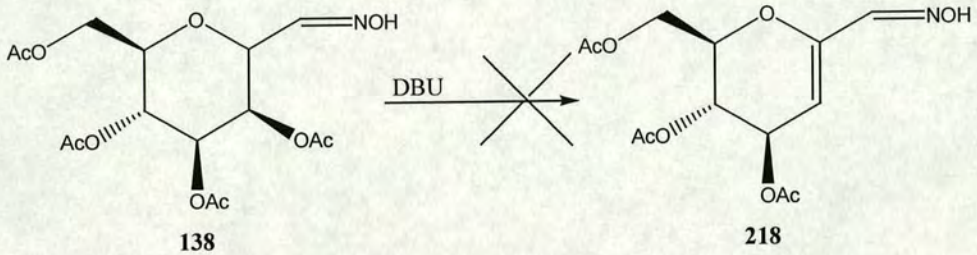
Scheme 97

Other electrophilic additions investigated include dihydroxylation using osmium tetroxide and hydroboration. However, initial attempts at these reactions failed and time constraints prevented further investigation.

The preliminary results described above suggest that a range of electrophilic additions should be possible thus providing access to a variety of functionalised pyranosyl isoxazolines.

2.12 Attempted synthesis of glycal nitrile oxide precursors

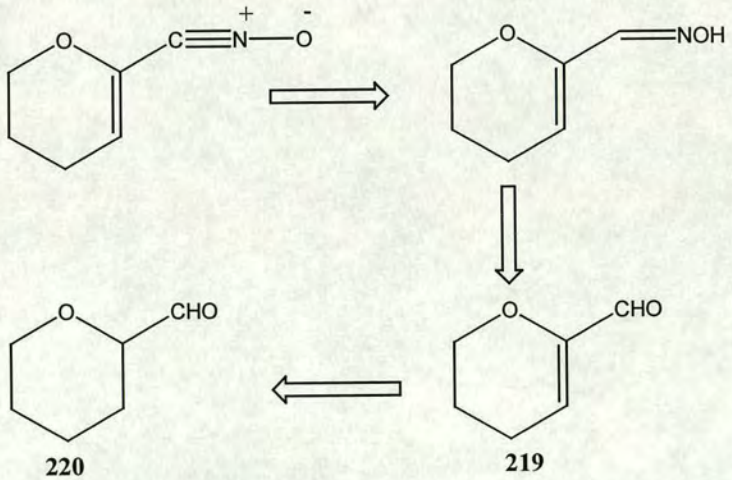
The discovery that under basic conditions pyranosylisoxazolines can undergo elimination reactions to afford glycal isoxazolines prompted an investigation into the possible synthesis of glycal nitrile oxide precursors, such as the α,β-unsaturated aldoxime (**218**). The initial approach considered involved treatment of pyranosylaldoximes such as (**138**) with DBU as base (Scheme 98). However, elimination products were not detected using this method so an alternative route was investigated.



138 **218**

Scheme 98

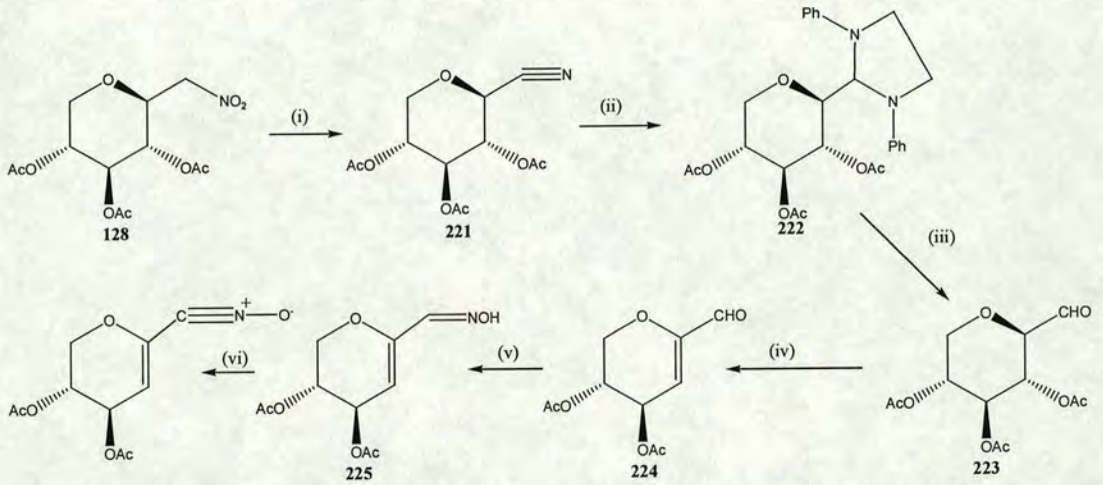
It was considered that a possible precursor to the α,β unsaturated oxime could be the glycal aldehyde (**219**) (Scheme 99). Synthesis of glycal aldehydes such as (**219**) from the corresponding saturated aldehyde (**220**) have been reported in the literature.[166] The formation of the α,β unsaturated aldehyde is made possible by strong conjugatory stabilising properties of the formyl group. Indeed, glycal aldehydes are often formed as by-products in the synthesis of *C*-formyl aldehydes.[101]



220 **219**

Scheme 99

The route selected was based on work of Moffat *et al*[130] and Lehmann *et al*[166] (Scheme 100). The first step was the synthesis the 2,3,4-tri-*O*-acetyl-xylopyranosylnitrile (**221**).The method adopted was based on observations by Koll *et al*[174] that treatment of pyranosylnitromethanes with phosphorous trichloride caused conversion to the nitrile. The pyranosylnitromethane chosen for study was 2,3,4-tri-*O*-acetyl-xylopyranosylnitromethane (**128**) due to the ease of synthesis. Treatment of (**128**) in pyridine with phosphorous trichloride gave a brown solution and, following an acidic work up, 2,3,4-tri-*O*-acetyl-xylopyranosylnitrile (**221**) was obtained as a white solid in 85% yield. The compound was characterised by ^{1}H and ^{13}C NMR spectroscopy by comparison with the literature values.[174]



(i) PCl_3, Py; (ii) Raney Ni, H_2, $PHNH_2CH_2CH_2NH_2Ph$; (iii) TsOH; (iv) Py / AcOH; (v) $NH_2OH.HCl$ (vi) NCS

Scheme 100

One-pot conversion of pyranosylnitriles into pyranosyl aldehydes has been reported by Schmidt *et al*[175] using Raney nickel catalysed hydrogenation of the nitrile, followed by hydrolysis of the resultant imine. However, this approach proved unsuccessful and an alternative approach was therefore considered. The formyl-*C*-glycoside was synthesised in two steps. Firstly a masked form of the aldehyde, the imidazolidine (**222**), was prepared using the method described by Lehmann *et al.*[166] 2,3,4-Tri-*O*-acetyl-xylopyranosylnitrile (**221**) was treated with Raney nickel in aqueous conditions in the presence of *N,N'*-diphenylethylenediamine and sodium hypophosphite. Imidazolidine (**222**) was separated from excess reagents and by-products by dry flash chromatography in 79% yield as a white solid. Characterisation was achieved using ^{1}H and ^{13}C NMR with signals at ~3.6 ppm in the ^{1}H spectrum corresponding to the two CH_2 groups of the imidazolidine ring and between 6.8

and 7.4 ppm due to the aromatic protons. The coupling between the anomeric proton (H-2) and the CH (H-1) of the imidazolidine ring is so small that the signal due to imidazolidine the ring proton appears as a singlet. The ^{13}C spectrum show peaks at 46.4 and 17.1 ppm due to the CH_2 groups of the imidazolidine ring and signals between 112.7 and 146.4 ppm due to the aromatic carbons. Unmasking of the aldehyde was achieved by treatment imidazolidine (**222**) with *p*-toluenesulfonic acid in acetone. The product (**223**) was obtained as a oil in a 60% yield. Characteristic peaks for the aldehydic proton were seen at 9.50 ppm in the ^1H spectrum and 196.0 ppm in the ^{13}C NMR.

The elimination of acetic acid was achieved under mild basic conditions by stirring aldehyde (**223**) in pyridine and acetic acid for 5 days. The glycal aldehyde (**224**) was obtained as an clear oil with a purple hue in 76% yield. The formation of the product was indicated in the ^1H NMR by the loss of one acetyl signal and a change in the position of the aldehydic signal to lower chemical shift due to the introduction of conjugation. The ^{13}C NMR showed a C-H signal at 113.0 ppm due to the C-3 olefinic hydrogen and a quaternary peak at 153.2 due to the anomeric carbons. The IR spectrum showed a peak at 1709 cm^{-1} characteristic of an α,β-unsaturated aldehyde and an absorption at 1643 cm^{-1} for of a C=C group in conjugation with an aldehyde.

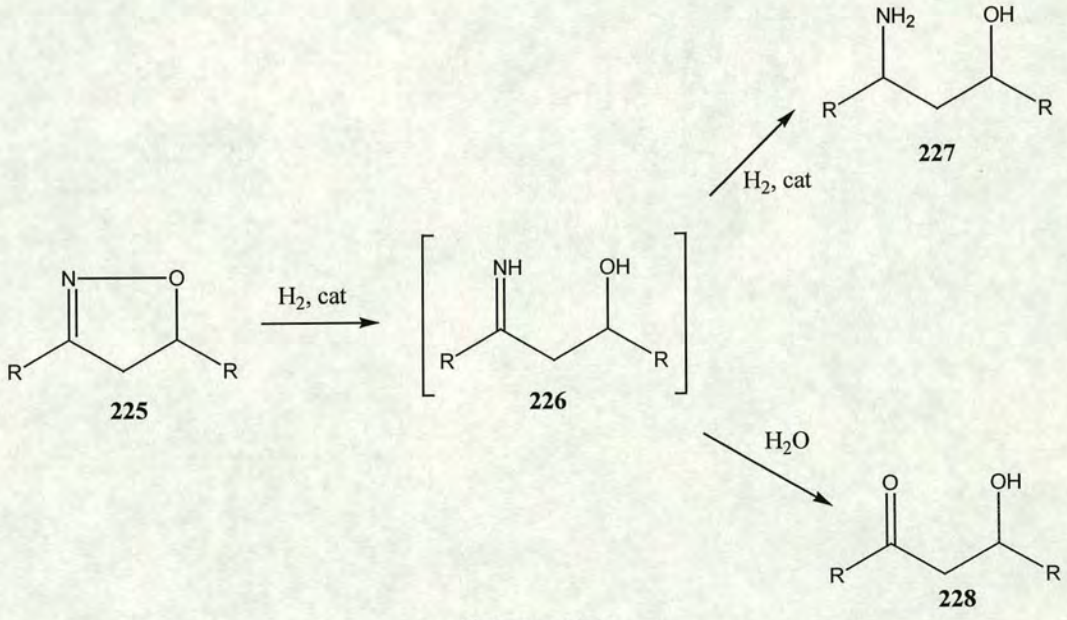
2.12.1 Attempted oximation of 4,5-tri-*O*-acetyl-2,6-anhydro-3-deoxy-*aldehydo*-*D*-*threo*-hept-2-enose (224)

Precedence for conversion of α,β-unsaturated aldehydes to the corresponding oximes had been set by Torssell *et al.*[176] In their work they describe the conversion of certain acyclic α,β-unsaturated aldehydes to the oximes, followed by conversion to the nitrile oxide using NCS and subsequent cylcoaddition to yield isoxazolines. The procedure used for oximation involved treatment of the aldehyde with hydroxylamine hydrochloride and sodium hydrogencarbonate in a two-phase system. However, attempts to apply this methodology to the pyranose system (**224**) gave complicated mixtures of products which proved impossible to separate. Thus far, other methods of oximation have not been investigated so the synthesis of the sugar-derived α,β-unsaturated oximes has not been achieved.

2.13 Ring opening reactions

The final step of the nitrile oxide / isoxazoline approach involves unmasking of the latent functionalities to give either the β-hydroxyketone or γ-aminoalcohol by ring opening of the isoxazoline. The product depends on the conditions used. In non-aqueous conditions the γ-aminoalcohol is obtained but, if the reaction is carried out in the presence of water, the β-hydroxyketone is formed.

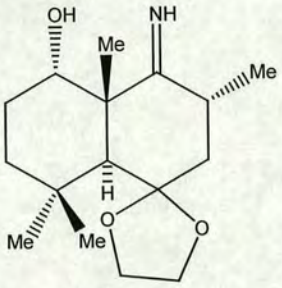
There are a number of methods in the literature for opening the 2-isoxazoline ring (**225**) (Section 1.2.3).[47] The most common approach involves catalytic hydrogenation using palladium on charcoal or Raney nickel.[47] The weak N-O bond is broken preferentially to the carbon heteroatom multiple bond leading to the β-hydroxyimine intermediate (**226**) (Scheme 101). In the absence of water the intermediate undergoes further reduction to give the γ-aminoalcohol (**227**) whilst in the presence of water the imine is hydrolysed to the β-hydroxyketone (**228**).



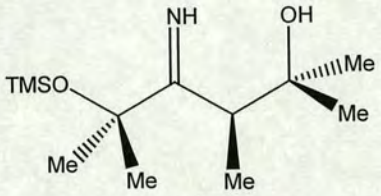
Scheme 101

For the formation of the γ-aminoalcohol an alternative mechanism involving initial reduction of the C=N bond has been proposed.[47] This is likely to be the case when ring opening to the γ-aminoalcohol using hydride reduction with $LiAlH_4$. However, when using catalytic hydrogenation the formation of the β-hydroxyimine intermediate is more likely.

Under the acid conditions often used the imine is generally not observed but in two cases isolation has proved possible, (**229**)[177] and (**230**),[178] thus supporting the proposed mechanism.

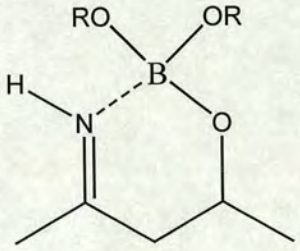


229



230

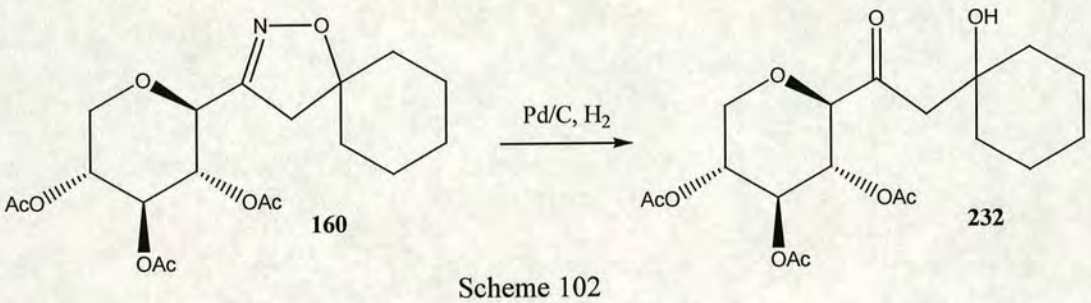
An in depth investigation into optimum conditions for ring opening has been carried out by Curran *et al.*[14] The usual reaction conditions for the formation of the β-hydroxyketone involve catalytic hydrogenation in an aqueous methanol solution under acidic conditions. The acid increases the rate of imine hydrolysis. This has a two-fold effect. Firstly, it increases the yield of β-hydroxyketone by reducing the time the imine spends in reductive conditions, thus minimising γ-aminoalcohol formations. Secondly, rapid hydrolysis reduces the chance of epimerisation that can occur. A variety of acids have been employed including acetic acid,[179] conc. HCl[50], aluminium[50] and boron trichlorides[180] and acetate and phosphate buffers.[181] These have been somewhat superseded by the use of boric acid,[14] as it is very effective at minimising epimerisation, possibly due to formation of a cyclic borate ester (**231**).



231

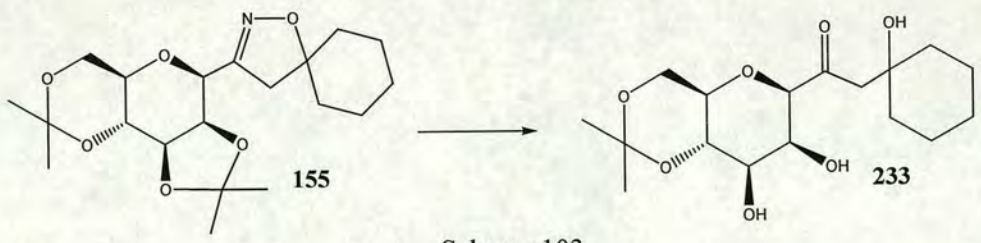
The application of these hydrogenolysis conditions within the group in the past has proved successful[120] although it is sometimes capricious The ring opening of **160** using H_2-Pd/C and **155** using Raney nickel proved successful.

Hydrogenation of (**160**) (Scheme 102) with Pd/C gave an oil that was shown by TLC to contain three products, which were separated by dry flash chromatography. The least polar spot was identified as unreacted starting material (**160**), whilst the baseline material proved impossible to characterise, although it gave a positive test with ninhydrin stain indicating that it may be the γ-aminoalcohol. The other spot was isolated in 14% yield and identified by ^{1}H NMR and ^{13}C NMR spectroscopy as the β-hydroxyketone (**232**). The ^{13}C NMR shows formation of (**232**) by the appearance of a quaternary peak at 207.3 ppm characteristic of a carbonyl group whilst the C=N peak at ~150 ppm of the isoxazoline is no longer apparent. In other respects the ^{1}H NMR was broadly similar to that of the parent isoxazoline. The mass spectrum contained a weak parent ion peak at 401 amu, but with a much stronger peak at 383 amu. This M-18 peak suggests elimination of water during ionisation in the spectrometer most likely leading to the formation of an α-enone.



Scheme 102

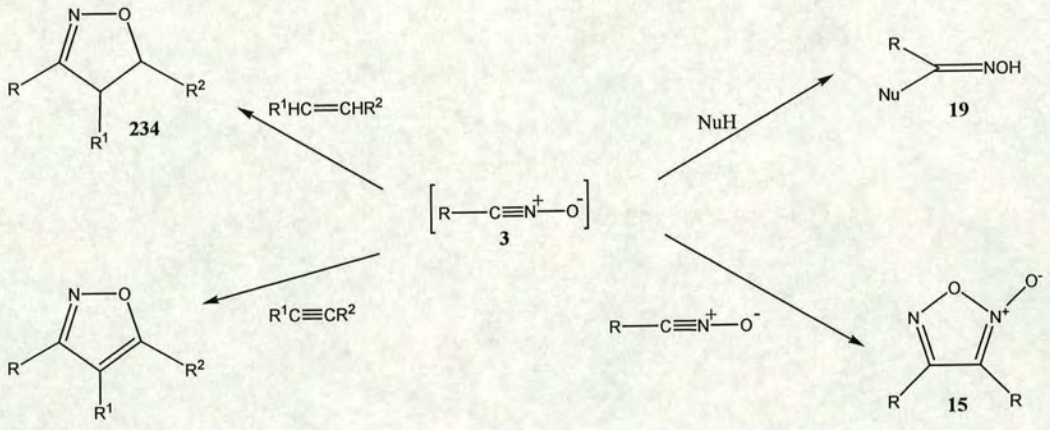
Hydrogenation of (**155**) with Raney nickel gave an oil which was purified by chromatography to give a baseline material and a less polar oil which was identified by ^{1}H and ^{13}C NMR to be the partially deprotected β-hydroxyketone in (62%) (**233**) (Scheme 103). The ^{13}C NMR again showed the characteristic carbonyl peak at 209.9. The absence of peaks at around 26, 28 and 110 ppm indicate the loss of the 1,3-dioxolane ring of the acetal protection. Again the ^{1}H spectrum was broadly similar to the parent isoxazoline except for the loss of one of the isopropylidene signals at around 1.5 ppm. High levels of fragmentation were seen in the mass spectrum preventing detection of a parent ion peak.



Scheme 103

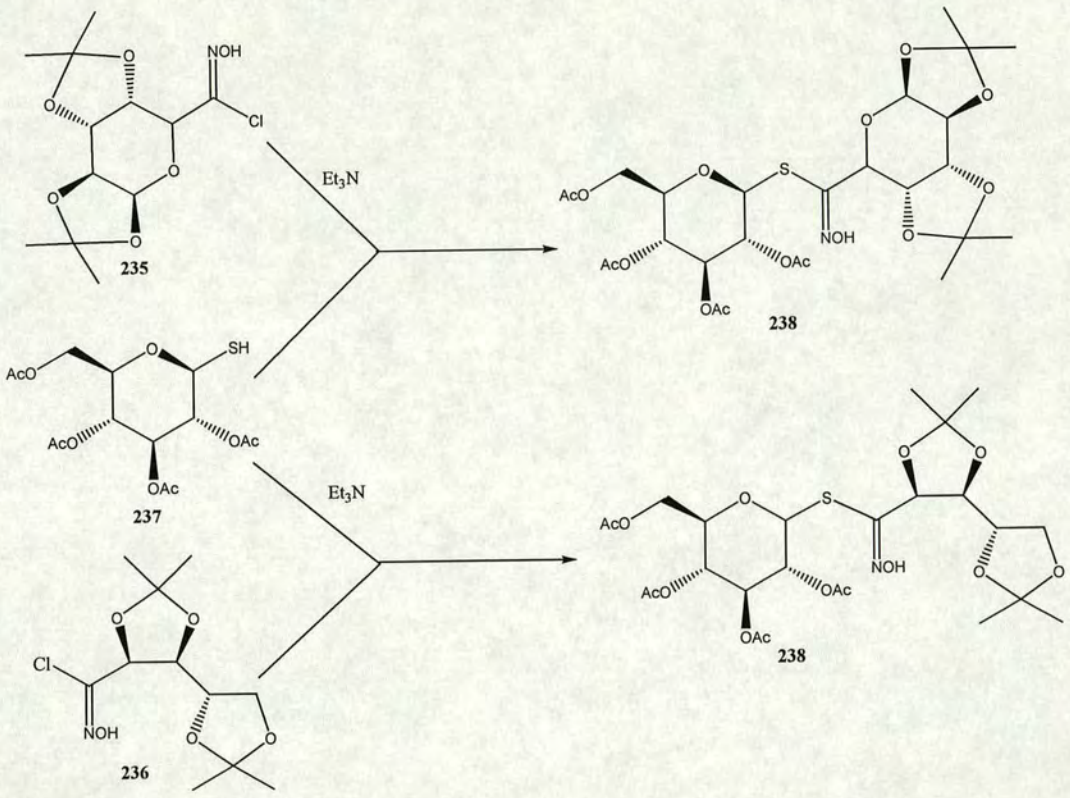
2.14 1,3-Addition reactions

Arguably the most common reactions of nitrile oxides (**3**) are cycloadditions to unsaturated systems to form 5-membered heterocycles, for example reaction with alkenes to give 2-isoxazolines (**234**) (Scheme 104). Indeed, much of the work reported in this thesis involves this type of reaction. Dimerisation of nitrile oxides to furoxans (**15**) is also common. However, nitrile oxides can undergo other reactions such as 1,3-addition with nucleophiles to afford substituted oximes (**19**).



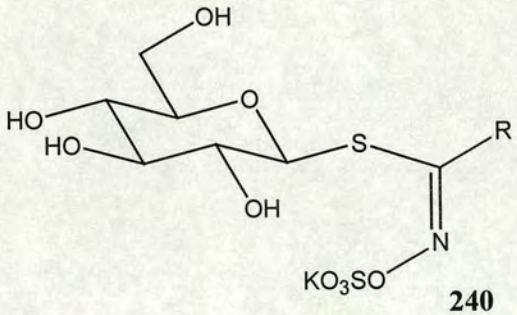
Scheme 104

Addition reactions have been reported for a variety of nucleophiles (NuH) including alcohols, thiols and amines.[3] The possible application of such 1,3-addition reactions in carbohydrate chemistry has been highlighted by work by Rollin *et al*[31] who have reported the formation of thiohydroximate-linked pseudodisaccharides by reaction of a 1-thio-D-glucose with various sugar-derived nitrile oxides. For example, the D-galactose-derived oxime (**235**) and D-xylose-derived oxime (**236**) were used as precursors to the corresponding nitrile oxides and reacted with a thioglucose (**237**) to afford adducts (**238**) and (**239**) as outlined in Scheme 105.



Scheme 105

These thiohydroximate-linked pseudodisaccharides are of interest themselves, but could also be precursors to glucosinolates, which are naturally occurring thiosugars found in the botanical order *Brassicales*.[31]

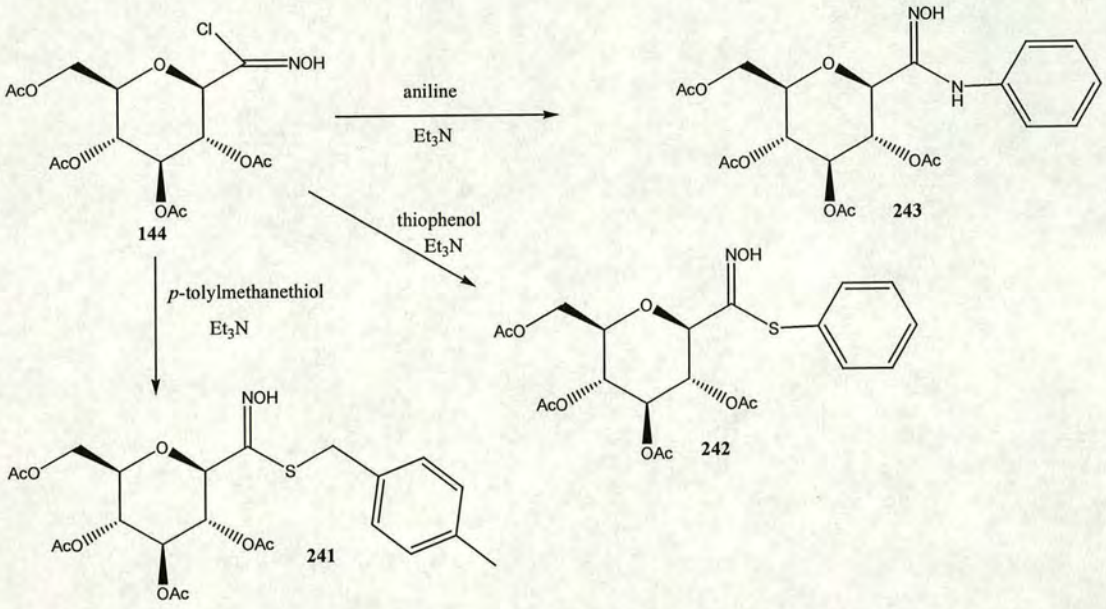


240

R = more that 100 varius aglycons

The work described by Rollin *et al*[31] was carried out on either acyclic sugar nitrile oxides or pyranose systems with the nitrile oxide at the non-reducing terminus of the sugar. Thus, the novel pyranosylhydroximoyl chlorides described in section 2.3, which should afford *C*-

glycoside analogues, appeared ideal candidates for investigation. Three nucleophiles, 4-tolylmethanethiol, thiophenol and aniline were used as model nucleophiles and addition reaction carried out with 2,3:4,6-tetra-O-acetyl-β-D-glucopyranosyl nitrile oxide (**115**) (Scheme 106).



Scheme 106

The general procedure involved the slow addition of triethylamine in dry ether to a solution of hydroximoyl chloride (**144**) and the thiol in dry ether over 24 hours. The product was isolated by aqueous work up and column chromatography.

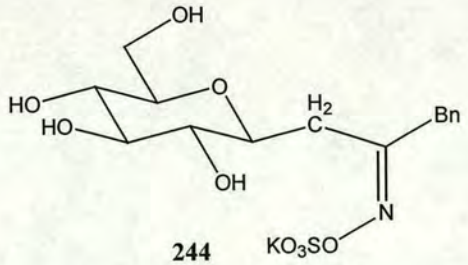
For the reaction of hydroximoyl chloride (**144**) and 4-tolylmethanethiol a white solid (79%) was obtained, which was shown by ^{1}H and ^{13}C NMR to be adduct (**241**) as a single isomer. The main feature of the ^{1}H NMR was a broad singlet at 8.96 ppm due to the C=NOH group with appropriate signals for the protons of the CH_3 group on the aromatic ring (2.35 ppm), the benzyl CH_2 group (4.20 ppm) and the aromatic ring (7.10 - 7.34 ppm). The ^{13}C spectrum showed the usual signals corresponding to the peracetyl pyranose ring along with aromatic peaks, peaks at 21.0 and 34.3 ppm due to the methyl and CH_2 groups and a diagnostic peak at 148.7 ppm for the C=NOH.

The product (**242**) of the reaction hydroximoyl chloride (**144**) with thiophenol was obtained in a 85% yield, with characterisation being achieved by NMR spectroscopy and mass spectrometry.

Formation of adducts (**241**) and (**242**) led to an investigation into alternative nucleophiles. Amines were selected as possible candidates with aniline chosen for study. To prevent high levels of nitrile oxide concentration and thus dimerisation to furoxan both aniline and triethylamine were added via syringe. The reaction of (**144**) with aniline produced an oil which was purified by dry flash chromatography to afford furoxan (**162**) (44%) and the adduct (**243**) (26 %). The latter product was characterised by ^{1}H and ^{13}C NMR which showed the presence of only one isomer. The C=NOH peak in the ^{1}H spectrum at 8.39 ppm was significantly broader than seen previously. The ^{13}C NMR contained the diagnostic peak at 146.5 ppm due to the C=NOH.

2.14.1 Summary and future work

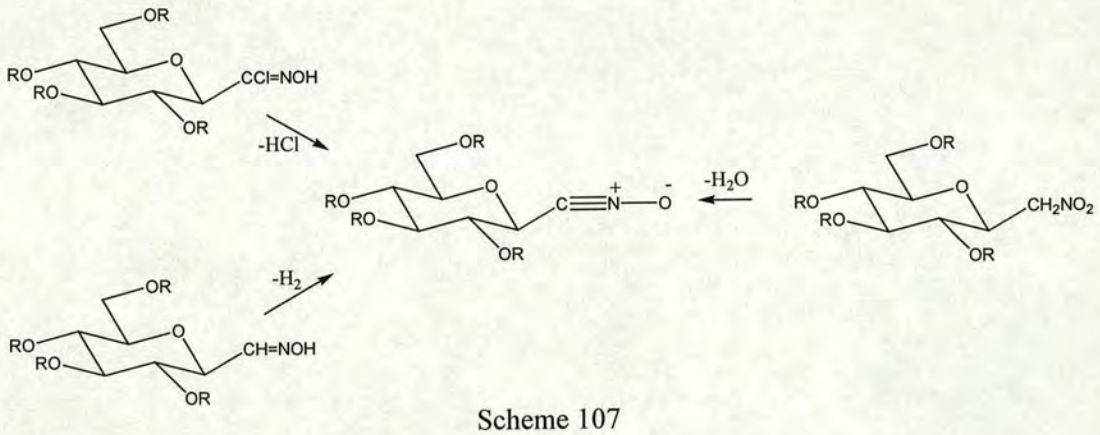
The initial investigation of 1,3-addition reactions has shown that there is potential for future work in the area. The successful reaction using aniline suggests the possible application of amino acids in the reaction. Alternatively, amino acids such as cysteine could be reacted through the sulfur atom. There is also the prospect of increasing the range of nucleophiles to include alcohols and phenols. Perhaps more importantly is the potential use of carbon-based nucleophiles such as Grignard reagents. Theses might allow access to non-hydrolysable pseudo-disaccharides. Similar compounds (e.g. (**244**)) have been synthesised by Rollin *et al*[182] using different methodology and have shown inhibition towards myrosinase. The use of these carbon-based nucleophiles may require alternative protection strategies. 3,4,5,7-Tetra-O-benzyl-β-D-glucopyranosyl hydroximoyl chloride discussed in section 2.3.2 could be an ideal candidate.



244

Conclusions and future work

The work presented in this thesis shows the synthetic utility of pyranosylnitrile oxides as precursors to pyranosyl isoxazolines and isoxazoles. Two novel routes to pyranosyl nitrile oxides have been developed involving oxidation of pyranosyl aldoximes and dehydrohalogenation of the corresponding hydroximoyl chlorides. These new routes complement the existing approach based on pyranosylnitromethanes (Scheme 107).



Scheme 107

Generation of the pyranosyl nitrile oxides in the absence of a dipolarophile affords 3,4-dipyranosylfuroxans in high yield. These nitrile oxide dimers, which were previously regarded as unwanted by-products, are of interest in there own right. They may have potential therapeutic applications as nitric oxide donors, and they have also been identified as precursors to carbon-linked disaccharides with functionalised bridges. Reduction leads to dipyranosyl glyoximes, which are of particular interest as novel chiral ligands for metal complexes. They are also precursors to heterocycles such as furazans and may provide access to dipyranosyl 1,2-diamines and 1,2-diketones.

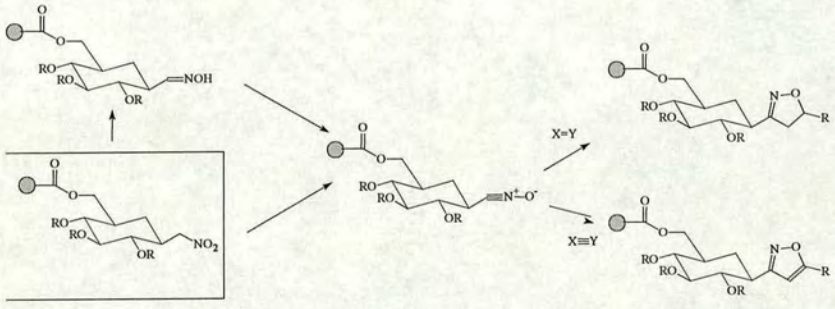
Substituted oximes have been formed by the 1,3-addition reactions of pyranosyl nitrile oxides, generated from the hydroximoyl chloride, with sulphur based- and nitrogen based-nucleophiles. Similar compounds have been reported to show inhibition of myrosinase.[182] The range of applicable nucleophiles needs to be investigated further.

Under basic conditions the pyranosyl isoxazoline have been shown to undergo elimination reactions to afford glycal isoxazolines. These compounds are susceptible to electrophilic

addition reactions at the glycal double bond and thus should provide access to a variety of analogues.

Initial investigations suggest that reductive ring opening of the isoxazolines afford β-hydroxyketones and γ-amino alcohols, although optimum conditions for the ring opening reactions have yet to be determined.

A possible area for future study is the transfer of this methodology to the solid phase. It is envisaged that the pyranoyslnitromethyl compound would be tethered to an appropriate linker through the hydroxyl group at the 6-position (Scheme 108). A major advantage of carrying out this work on the solid phase would be the prevention of nitrile oxide dimerisation.



Scheme 108

3 Experimental

3.1 General

3.11 Instrumentation

^{1}H and ^{13}C NMR were recorded on Bruker ARX250 and Bruker avance 360 instruments by Mr J. R. A. Miller and Mr W. Kerr. High field ^{1}H NMR was carried out on a Varian inova 600 instrument by Dr I. Sadler. Two dimensional spectra were typically recorded on the Bruker avance 360 instrument. Chemical shifts (δ) in all spectra are measured in parts per million using tetramethysilane ($\delta = 0.0$) as the reference signal

Fast Atom Bombardment (FAB) mass spectra and exact mass measurement were recorded using a Kratos MS50TC instrument using either glycerol or thioglycerol as a matrix by Mr A. Taylor.

Melting points were measured on a Gallenkamp capillary tube apparatus and are uncorrected. Optical rotations were measured on an Optical Activity Polaar 20 polarimeter using 5 cm^3 of filtered solution. IR spectra were obtained as liquid films or nujol mulls on a Perkin Elmer Paragon 1000 FT-IR spectrometer and are quoted in wavenumbers (cm^{-1}).

The X-ray structural analysis of (**138**), (**164**) and (**200**) were carried out by Dr S. Parsons,

3.1.2 Chromatography

Analytical thin layer chromatography was carried out using Merck aluminium-backed plates with Kiesegel GF_{254} (0.2 mm).

Dry flash chromatography was performed using sintered funnels of various diameters filled with Kieselgel GF_{254} and eluted under a water pump vaccuum.

Medium pressure liquid chromatography was carried out using two 1metre columns packed with Kieselgel 60. Elution was performed at a pressure of 40-50 psi.

High pressure liquid chromatography was carried out on a Gilson instrument fitted with a refractive index detector using a Varian dynamax (250 mm x 21.4 mm) column packed with microsorb 100 silica.

3.1.3 Solvents and reagents

All reagents and solvents were standard laboratory grade and were used as supplied unless otherwise stated.

Dry ether and toluene were Analar grade dried over sodium wire.
Dry chloroform was obtained by distillation from calcium chloride and stored over 4Å molecular sieves.
Dry pyridine was Analar grade distilled from and stored over potassium hydroxide.
Dry THF and ethylene glycol diethylether was freshly distilled from calcium hydride.
Acetic anhydride was purified by fractional distillation and stored over 4Å molecular sieves.

3.2 Synthesis of nitrile oxide precursors

3.2.1 Acetylated 2,6-anhydro-1-deoxy-1-nitroalditols

These compounds were prepared from D-glucose (**246**) and D-mannose (**123**) by a modified version of the procedure of Köll *et al*[106] by base catalysed addition of nitromethane to the parent monosaccharide.

3.2.1.1 1-Deoxy-1-nitroalditols

The title compounds were prepared from the corresponding aldoses by a modified version of the Fischer-Sowden reaction[106] using the general procedure below.

GENERAL PROCEDURE: The monosaccharide (1 equiv.) was dissolved in methanol (50 cm^3) and to this nitromethane (12 equiv.) was added under anhydrous conditions in a nitrogen atmosphere. A freshly prepared solution of sodium methoxide in methanol, made by dissolving sodium (1.3 equiv.) in dry methanol (175 cm^3), was added drop-wise and the reaction mixture was allowed to stir overnight. The solid formed was isolated by filtration,

washed with ice cold methanol, and dissolved in ice cold water. The solution was then rapidly forced through an amberlite IR 120 (H^+) ion exchange column.* Excess nitromethane was removed by rotary evaporation at reduced pressure until sufficient water distilled over to achieve complete removal of nitromethane.

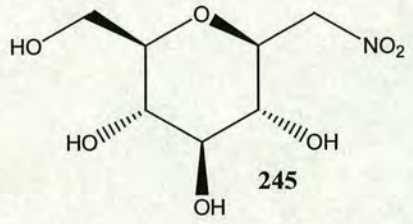
3.2.1.2 2,6-Anhydro-1-deoxy-1-nitroalditols

These compounds were prepared by acid-catalysed cyclisation of 1-deoxy-1-nitroalditols using a modified literature procedure.[106]

GENERAL PROCEDURE: The solution of the 1-deoxy-1-nitroalditol was heated at reflux overnight, then treated with activated charcoal and heated at reflux for a further two hours. The charcoal was then removed by filtration through a celite pad and the solvent removed *in vacuo* to give an oil. The product was isolated as a white crystalline solid by continuous liquid/liquid extraction using ethyl acetate / water (48 hours), followed by concentration of the organic layer *in vacuo*.

3.2.1.2.1 Synthesis of 2, 6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol (β-D-glucopyranosylnitromethane) (245)

Sample code: KWB01
Molecular formula: $C_6H_{13}NO_7$
Molecular weight: 223



245

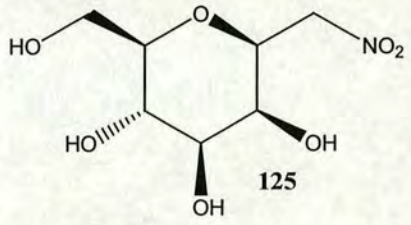
D-Glucose (**246**) (30.57 g, 0.17mol, 1 equiv.) was dissolved in a mixture of methanol (50 cm^3) and nitromethane (90 cm^3, 2 mmole, 12 equiv.) and reacted with sodium methoxide (5.2 g, 0.22 mmole, 1.3 equiv. sodium in 175 cm^3 dry methanol). Following the procedure described above, compound (**245**) was isolated (6.6 g, 17%); mp 173-175°C (lit.[106] 175-176°C); $[\alpha]^{18}_D$ +20.0 (c = 1.0, H_2O); δ_H (360 MHz, D_2O) 3.23-3.46 (4H, m, 3-H, 4-H, 5-H, 6-H), 3.58 (1H, dd, 7a-H), 3.75 (1H, dd, 7b-H), 3.99 (1H, ddd, 2-H), 4.58 (1H, dd, 1a-H), 4.85 (1H, dd, 1b-H); J(x-y)/Hz 1a-1b 13.5, 1a-2 2.6, 1b-2 8.7, 2-3 10.0, 3-4 nd, 4-5 nd, 5-6

* The column was prepared by washing through with water until any colouration disappeared. The amberlite was then acidified by addition of 1M HCl. Water was then passed through until the pH returned to pH 4.

nd, 6-7a 1.9, 6-7b 5.1, 7a-7b 12.4; δ_C (90 MHz, $CDCl_3$) 60.6 (C-7), 79.4, 70.5, 76.0, 77.1, 79.6, (C-2, C-3, C-4, C-5, C-6), 76.6 (C-1); *m/z* (FAB) Found: M^++H, 224.07734. $C_7H_{14}NO_7$ requires M^++H 224.07703.

3.2.1.2.2 Synthesis of 2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (β-D-mannopyranosylnitromethane) (125)

Sample code: KWB03
Molecular formula $C_7H_{13}NO_7$
Molecular weight: 223



125

D-Mannose (**123**) (13.0 g, 72.2 mmole, 1 equiv.) was dissolved in methanol and nitromethane (50 cm^3, 0.72 mole 10 equiv.) and reacted with a methanolic sodium methoxide solution (2.21 g, 96.1 mmole, 1.33 equiv. sodium in 80 cm^3 dry methanol). Following the procedure outlined above the product (**125**) was obtained as a white crystalline solid (4.99 g, 31%); mp 151-152°C (lit.[106] 151-152°C); $[\alpha]_D^{18}$ = -33 (*c* = 1, H_2O); δ_C (63 MHz, D_2O) 61.0 (C-7), 66.8, 69.3, 73.6, 74.7, 80.0 (C-2, C-3, C-4, C-5, C-6), 76.5 (C-1); *m/z* (FAB) Found: M^++H, 224.07716. $C_7H_{13}NO_7$ requires M^++H 224.07703.

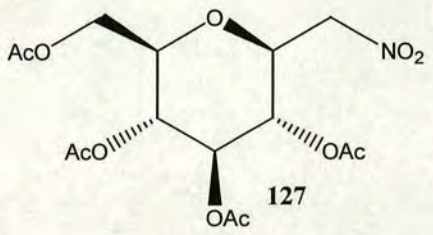
3.2.1.3 Acetylated 2,6-anhydro-1-deoxy-1-nitroalditols

The acetylation of 2,6-anhydro-1-deoxy-1-nitroalditols was carried out by the method of Köll *et al.*[106]

GENERAL PROCEDURE: The 2,6-anhydro-1-deoxy-1-nitroalditol (1 equiv.) was dissolved in dry acetic anhydride (100 equiv.) under anhydrous conditions in a nitrogen atmosphere and cooled to 0°C (ice bath). To this a catalytic amount of trifluormethanesulfonic acid (0.1 cm^3) was added and the reaction mixture allowed to stir overnight. The solution was then poured into ice cold water, extracted with chloroform (3 x 50 cm^3) and the organic portion dried ($MgSO_4$). Removal of solvent *in vacuo* yielded the product as a white solid, which was further purified by recrystallisation from the appropriate solvent.

3.2.1.3.1 Synthesis of 3, 4, 5, 7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol (3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylnitromethane) (127)

Sample code: KWB02
Molecular formula: $C_{15}H_{21}NO_{11}$
Molecular weight: 391

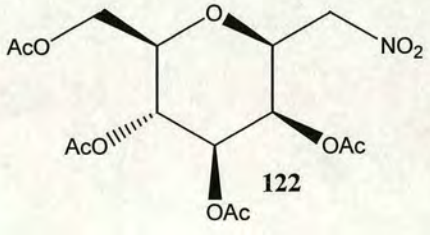


127

Using the procedure outlined above, β-D-glucopyranosylnitromethane (**245**) (500 mg, 2.24 mmole, 1 equiv.) was dissolved in dry acetic anhydride (20 cm^3, 0.21 mole, 100 equiv.) and trifluormethanesulfonic acid (0.1 cm^3) added. The product (**127**) was recrystallised from ethanol to give a white solid (0.70 g, 80%); mp 143-145°C (lit.[106] 144 -145°C); $[\alpha]_D^{18}$ = +15.0 (*c* = 0.4, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.95, 1.97, 2.00, 2.01 (12H, 4 x s, 4 x $COCH_3$), 3.70 (1H, ddd, 6-H), 3.99 (1H, dd, 7a-H), 4.21 (1H, dd, 7b-H), 4.24 (1H, dd, 2-H), 4.36 (1H, dd, 1a-H), 4.48 (1H, dd, 1b-H), 4.88 (1H, dd, 3-H), 5.01 (1H, dd, 5-H), 5.21 (1H, dd, 4-H); *J*(x-y)/Hz 1a-1b 13.7, 1a-2 2.9, 1b-2 8.8, 2-3 10.1, 3-4 9.3, 4-5 9.3, 5-6 10.0, 6-7a 2.3, 6-7b 4.9, 7a-7b 12.5; δ_C (90 MHz, $CDCl_3$) 20.3, 20.4 (4 x $COCH_3$), 61.4 (C-7), 67.7, 69.0, 73.3, 74.1, 75.5 (C-2, C-3, C-4, C-5, C-1), 75.7 (C-6), 169.1, 169.5, 169.8, 170.3 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H 392.11964 $C_{15}H_{22}NO_{11}$ requires M^++H 392.11929.

3.2.1.3.2 Synthesis of 3, 4, 5, 7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylnitromethane) (122)

Sample code: KWB07
Molecular formula: $C_{15}H_{21}NO_{11}$
Molecular weight: 391



122

Following the general procedure outline above, β-D-mannopyranosylnitromethane (**125**) (936 mg, 4.20 mmole, 1 equiv.) was dissolved in dry acetic anhydride (40 cm^3, 0.414 mole, 100 equiv.) and trifluormethanesulfonic acid (0.1 cm^3) added. The product (**122**) obtained was recrystallised from ethanol to give a white solid (1.44 g, 92%); mp 180-181°C (lit.[106]

179-180°C); $[\alpha]_D^{18}$ = -33 (*c* = 1 in $CHCl_3$) {lit.[106] $[\alpha]_D^{18}$ = -32 (*c* = 1 in $CHCl_3$)}; δ_H (360 MHz, $CDCl_3$) 1.98, 2.04, 2.06, 2.18 (12H, 4 x s, 4 x $COCH_3$), 3.71 (1H, ddd, 6-H), 4.05 (1H, dd, 7a-H), 4.27 (1H, dd, 7b-H), 4.39 (1H, dd, 1a-H), 4.46-4.54 (2H, m, 1b-H, 2-H), 5.09 (1H, 4-H), 5.24 (1H, dd, 5-H), 5.43 (1H, dd, 3-H); *J*(x-y)/Hz 1a-1b 13.0, 1a-2 1.8, 1b-2 9.2, 2-3 0.7, 3-4 3.4, 4-5 10.0, 5-6 10.0, 6-7a 2.3, 6-7b 5.7, 7a-7b 12.4; δ_C (90 MHz, $CDCl_3$) 20.9, 21.0, 21.0, 21.1 (4 x $COCH_3$), 62.7 (C-7), 65.9, 68.6, 72.1, 73.8, 76.9 (C-2, C-3, C-4, C-5, C-6), 75.6 (C-1), 170.0, 170.4, 170.6, 171.0 (4 x $COCH_3$); *m/z* (FAB) Found: M+H 392.11943 $C_{19}H_{22}NO_{11}$ requires 392.11929.

3.2.1.4 *In situ* acetylation of 2,6-anhydro-1-deoxy-1-nitroalditols

The synthesis of acetylated 2,6-anhydro-1-deoxy-1-nitroalditols without the isolation of the 2,6-anhydro-1-deoxy-1-nitroalditols was carried out for D-xylose and L-fucose as described in the general procedure below.

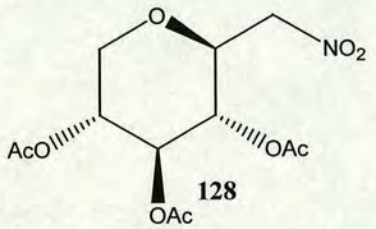
GENERAL PROCEDURE: To a stirred suspension of the parent monosaccharide (1 equiv.) in nitromethane (10 equiv.) and methanol (50 cm^3) was added sodium methoxide (1.3 equiv.) in methanol, and the mixture stirred for 16 h. The resulting solid was isolated by filtration, washed with cold methanol, and dissolved in cold water. After passing through an amberlite IR (H^+) ion exchange column, the solution was concentrated *in vacuo* to remove excess nitromethane. The resulting solution was heated under reflux for ~16 h, treated with activated charcoal, and heated at reflux for a further 2 h. After filtration to separate the charcoal, the solvent was removed *in vacuo* to afford an oil, which was treated under nitrogen with dry acetic anhydride (100 equiv.) and a catalytic amount of trifluoromethanesulfonic acid (0.1 cm^3). The mixture was stirred for ~16 h. The resulting solution was poured onto ice cold water and the product extracted into chloroform (3 x 20 cm^3), the organic portion dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude syrup formed was co-evaporated with toluene (3 x 10 cm^3) and the solvent removed *in vacuo* to afford the product.

3.2.1.4.1 Synthesis of 3,4,5-tri-*O*-acetyl-2,6-anhydro-1-deoxy-1-nitro-D-gulo-hepitol (3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane) (128)

Sample code: KWB69

Molecular formula: $C_{12}H_{17}NO_9$

Molecular weight: 319



128

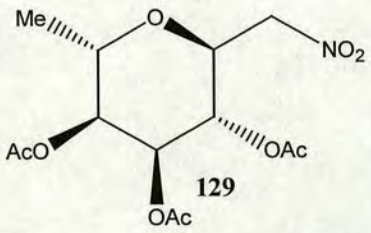
To a stirred suspension of D-xylose (**247**) (2.00 g, 1.3 mmole) in nitromethane (7.2 cm^3, 13 mmole, 10 equiv.) and methanol (5 cm^3), was added sodium methoxide (380 mg, 1.63 mmole, 1.25 equiv.) in methanol (10 cm^3). Following the general procedure outlined above a red oil was obtained which was purified by passing as a solution in ether through a pad of silica. Trituration with ethanol and recrystallisation from the same solvent gave the product (**128**) as a white solid (2.90 g, 68%); mp 164 – 166 °C (lit.[106] 164 – 165 °C); δ_H (250 MHz, $CDCl_3$) 2.30, 2.33 (9H, 3 x s, 3 x $COCH_3$), 3.61 (1H, dd, 6a-H),4.40 (1H, dd, 6a-H), 4.44 (1H, 2-H), 4.67 (1H, dd, 1a-H), 4.76 (1H, dd, 1b-H), 5.15 (1H, dd, 3-H), 5.26 (1H, dd, 5-H), 5.52 (1H, t, 4-H); *J*(x-y)/Hz 1a-1b 13.4, 1a-2 3.0, 1b-2 8.9, 2-3 10.1, 3-4 9.3, 4-5 9.4, 5-6a 5.7, 5-6b 10.6, 6a-6b 11.3; δ_C (63 MHz, $CDCl_3$) 21.0, 21.0, 21.2 ($COCH_3$), 67.1 (C-6), 69.0, 69.9, 73.5, 75.4 (C-2 to C-5), 76.4 (C-1), 170.2, 170.2, 170.6 ($COCH_3$).

3.2.1.4.2 Synthesis of 3,4,5-tri-*O*-acetyl-2,6-anhydro-1,7-dideoxy-1-nitro-L-*glycero*-D-*manno*-hepitol (3,4,5-tri-*O*-acetyl-β-L-fucopyranosylnitromethane) (129)

Sample code: KWB71

Molecular formula: $C_{13}H_{19}NO_9$

Molecular weight: 333



129

To a stirred suspension of L-fucose (**248**) (600 mg, 3.7 mmole), in nitromethane (2 cm^3, 36.5 mmole, 10 equiv.) and methanol (2 cm^3) was added sodium methoxide (0.1 mg, 4.4 mmole, 1.2 equiv.) in methanol (5 cm^3). Following the general procedure outlined above, the desired product (**129**) was isolated as a white solid (800 mg, 70%); mp 127-128 °C (from ethanol); (Found: C, 46.9; H, 5.5; N, 3.9. $C_{13}H_{20}NO_9$ requires C, 46.9; H, 5.8; N, 4.2); $[\alpha]_D^{18}$ -35.0 (*c* = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.14 (3H, d, 7-H), 1.97, 2.06, 2.16 (9H, 3 x s, $COCH_3$), 3.83 (1H, dq, 6-H), 4.20 (1H, ddd, 2-H), 4.35 (1H, dd, 1a-H), 4.54 (1H, dd, 1b-H), 5.02-5.12

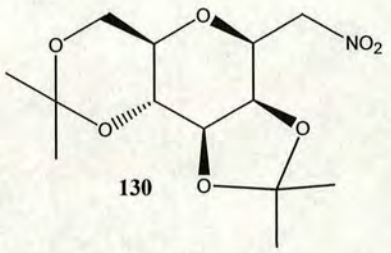
(2H, m, 3-H, 4-H), 5.27 (1H, dd, 5-H); *J*(x-y)/Hz 1a-1b 13.3, 1a-2 2.7, 1b-2 9.2, 2-3 9.8, 4-5 2.7, 5-6 1.1, 6-7 6.4; δ_C (63 MHz, $CDCl_3$) 16.0 (C-7), 20.5, 20.5, 20.6 ($COCH_3$), 66.7, 70.2, 71.8, 73.0, 74.6 (C-2 – C-6), 76.1 (C-1), 169.9, 170.0, 170.3 ($COCH_3$); *m/z* (FAB) Found: M^++1, 334.11398. $C_{13}H_{20}NO_9$ requires M^++H 334.11381.

3.2.2 Acetonation of 2,6-anhydro-1-deoxy-1-nitroalditols

The introduction of acetal protection was carried out using the procedure of Köll *et al.*

3.2.2.1 Synthesis of 3,4:5,7 di-*O*-isopropylidene-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol (3,4:5,7-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane) (130)

Sample code: KWB74
Molecular formula: $C_{13}H_{21}NO_7$
Molecular weight: 303



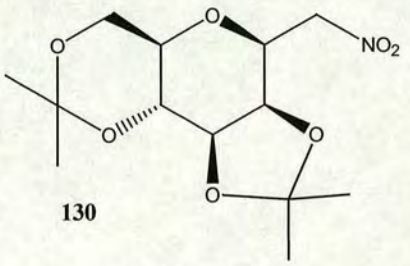
130

β-D-Mannopyranosylnitromethane (**125**) (100 mg, 0.448 mmole), dried $CaSO_4$ (0.25 g) and powdered toluenesulfonic acid (10 mg, 0.054 mmole) were suspended in dry DME (5 cm^3) and the mixture stirred for 15 minutes under anhydrous conditions in a nitrogen atmosphere. To this 2-methoxypropene (0.5 cm^3, 5 mmole) was added and the mixture stirred for a further 15 minutes. $NaHCO_3$ (0.1 g) was then added to the red solution and the resulting yellow solution filtered. The solvent was removed *in vacuo* to give an oil which afforded the product (**130**) on purification by dry flash chromatography (ether/hexane) (86 mg, 63%); mp 159-161°C (from ethanol) (lit.[128] 148-150°C); δ_H (250 MHz, $CDCl_3$), 1.31, 1.39, 1.47, 1.51 (12H, 4 x s, 4 x CH_3), 3.15 (1H, ddd, 6-H), 3.68 (2H, m, 5-H, 7'-H), 3.87 (1H, dd, 7-H), 4.11 (1H, dd, 4-H), 4.21 (1H, dd, 3-H), 4.54 (2H, m, 2-H, 1'-H), 4.68 (1H, dd, 1-H); *J*(x-y)/Hz 1-1' 14.1, 1-2 9.9, 1'-2 2.9, 2-3, 2.5, 4-3 5.4, 5-4 7.9, 6-5 10.1, 7-6 5.7, 7'-6 10.1,7'-7 10.9; δ_C (63 MHz, $CDCl_3$) 18.6, 26.2, 28.1, 28.8 (4 x CCH_3), 61.4 (C-7), 69.3, 72.4, 72.9, 73.6, 75.9 (C-2 to C-6), 75.8 (C-1), 99.6 (CCH_3), 110.3 (CCH_3).

Improved yields were obtained using a modified version of that reported by Köll *et al.*

3.2.2.2 Synthesis of 3,4:5,7 di-*O*-isopropylidene-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*galacto* heptitol (3,4:5,7-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane) (130)

Sample code: KWB257
Molecular formula: $C_{13}H_{21}NO_7$
Molecular weight: 303



130

β-D-Mannopyranosylnitromethane (**125**) (1.0 g, 4.48 mmole), Na_2SO_4 (2.5 g) and powdered toluene sulfonic acid (100 mg, 0.536 mmole) were suspended in dry DME (15 cm^3) and the mixture stirred for 15 minutes under anhydrous conditions in a nitrogen atmosphere. To this 2-methoxypropene (2.9 cm^3, 30.28 mmole) was added and the mixture stirred for a further 15 minutes. $NaHCO_3$ (1.0 g) was then added to the red solution and the resulting yellow solution filtered. Removal of solvent *in vacuo* gave an oil which on addition of hexane yielded a white solid. Recrystallisation from ethanol gave the desired product (**130**) as a white solid (1.1g, 81%). For analysis see section 3.2.2.1.

3.2.3 Benzyl ether protection

3.2.3.1 Synthesis of 3, 4, 5, 7-tetra-*O*-benzyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*- D-*gulo*-heptitol (3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane) (131)

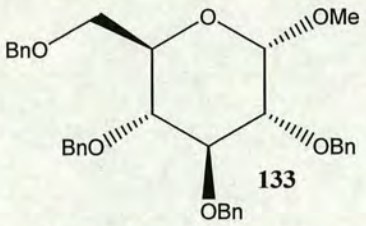
The target compound (**131**) was synthesised from methyl α-D-glucopranoside (**132**) in a 3 step synthesis. Conversion of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**134**) to 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (**131**) was achieved using the method of Best *et al.*[129]

3.2.3.1.1 Synthesis of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (133)

Sample code: KWB168

Molecular formula: $C_{35}H_{38}O_6$

Molecular weight: 554



133

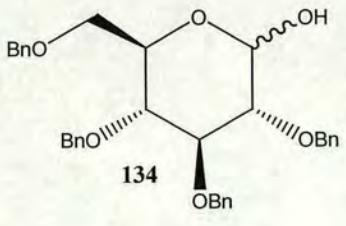
To a suspension of sodium hydride (60% w/w, 88 mg, 22 mmole) in anhydrous DMF (20 cm^3) cooled to 5°C was added a solution of methyl α-D-glucopyranoside (**132**) (500 mg, 2.75 mmole) in DMF (20 cm^3) over 30 mins. and the mixture stirred for 1 hour and allowed to warm to room temperature. After re-cooling to 5°C, benzyl bromide (2.8 g, 16.5 mmole) was added in three portions *via* syringe and the reaction stirred for 20 hours. Excess Sodium hydride was quenched carefully with methanol (10 cm^3), toluene (20 cm^3) and water (20 cm^3) added, and the aqueous layer extracted with toulene (2 x 50 cm^3). The combined organic layers were washed with water (20 cm^3), brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. Addition of triethylamine (1 cm^3) to the crude oil followed by stirring for 1 hour converted excess BnBr into benzyl triethylammonium bromide which was removed by partitioning the mixture between ether (50 cm^3) and water (50 cm^3). The organic portion was washed with brine (20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was purified by column chromatography (eluting from ether/hexane) to give the product (**133**) as a colourless oil (770 mg, 52%); δ_H (250 MHz, $CDCl_3$) 3.39 (3H, s, OCH_3), 3.52 (1H, dd, $J_{1\text{-}2}$ 3.6, $J_{2\text{-}3}$ 9.6, 2-H), 3.62 – 3.79 (4H, m, 4-H, 5-H, 6a-H, 6b-H), 4.00 (1H, t, $J_{2\text{-}3}$ 9.5, $J_{3\text{-}4}$ 8.8), 4.46 – 5.02 (8H, m, $ArCH_2$), 4.64 (1H, d, 1-H), 7.13 – 7.40 (20H, m, ArH); δ_C (63 MHz, $CDCl_3$) 55.0 (OCH_3), 68.3 (C-6), 73.2, 73.3, 74.9, 75.6 ($ArCH_2$), 69.9, 77.5, 82.0 (C2 - C5), 98.1 (C1), 127.5, 127.8, 127.8, 128.0, 128.2 (ArH), 137.8, 138.0, 138.1, 138.2 (ArC).

3.2.3.1.2 Synthesis of 2,3,4,6-tetra-*O*-benzyl-D-glucose (134)

Sample code: KWB215

Molecular formula: $C_{34}H_{36}O_6$

Molecular weight: 540



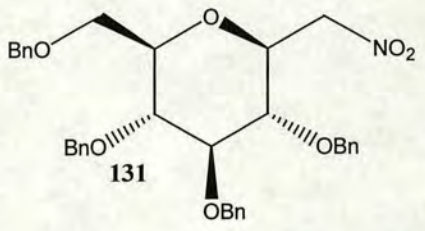
134

To a solution of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**133**) (3.07 g, 5.7 mmole) in glacial acetic acid (40 cm^3) was added 2M aqueous sulfuric acid (20 cm^3, 39.5

mmole) and the mixture stirred at 90°C for 18 hours. After cooling to room temperature, the acetic acid was removed *in vacuo*, the resulting oil diluted with DCM (50 cm^3) and the organic layer washed with saturated aq. $NaHCO_3$ (25 cm^3), brine (25 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a white solid which was recrystallised from methanol to afford the title compound (**134**) as a white crystalline solid (1020 mg, 33%); δ_H (250 MHz, $CDCl_3$) 1.81 (1H, br s, OH), 3.42 – 4.13 (12H, m, α2-H to α6-H, β2-H to β6-H), 4.50 – 5.03 (17H, m, α$ArCH_2$, β $ArCH_2$, β1-H), 5.29 (1H, d, $J_{1\text{-}2}$ 3.1, α1-H), 6.80 – 7.70 (40H, m, αAr, βAr); δ_C (63 MHz, $CDCl_3$) 69.0 (αC6), 69.3 (βC6), 73.9, 75.2, 75.5, 76.2 (α$ArCH_2$) 70.6, 78.2, 80.4, 82.2 (αC2 - αC5), 91.7 (αC1), 97.7 (βC1), 128.1 – 129.0 (ArH), 138.2 – 139.1 (ArC).

3.2.3.1.3 Synthesis of 3,4,5,7-tetra-*O*-benzyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-hepitol (3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane) (131)

Sample code: KWB176
Molecular formula: $C_{35}H_{37}NO_7$
Molecular weight: 583



131

Using the procedure of Best *et al*[129] nitromethane (6 cm^3) and diaminoethane (0.034 cm^3, 0.5 mmole) were added to a solution of tetra-*O*-benzyl-D-glucopyranose (**134**) (270 mg, 0.5 mmole) in DMSO (4 cm^3) and the mixture stirred at 80°C for 5 days. A further equivalent of diaminoethane was added and the mixture heated for another 4 days. The reaction mixture was extracted with chloroform (3 x 50 cm^3), the organic layer washed with water (2 x 50 cm^3), brine (2 x 50 cm^3) and then dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil which was purified by dry flash chromatography (eluting from ether/hexane) to yield the product (**131**) as an oil (210 mg, 72%) which partially solidified on standing; mp 80-81°C (lit 82-83°C); δ_H (250 MHz, $CDCl_3$) 3.41 (1H, dd, $J_{2,3}$ 9.8 $J_{3,4}$ 8.6 3-H), 3.52 (1H, m, 6-H), 3.69 – 3.85 (4H, m, 4-H, 5-H, 7a-H, 7b-H), 4.04 (1H, ddd, $J_{1a,2}$ 8.6, $J_{1b,2}$ 2.8, $J_{2\text{-}3}$ 9.8, 2-H), 4.30 – 4.67 (10H, m, 1a-H, 1b-H, $ArCH_2$), 7.16 – 7.44 (20H, m, ArH); δ_C (63 MHz, $CDCl_3$) 67.9 (C7), 71.2, 73.2, 74.7, 74.8 ($ArCH_2$), 76.4 (C1), 75.4, 76.9, 77.2, 78.9 (C3 – C6), 86.7 (C2), 127.5, 127.6, 128.0, 128.2, 128.3, 128.5 (ArH), 137.1, 137.7, 137.9 (ArC).

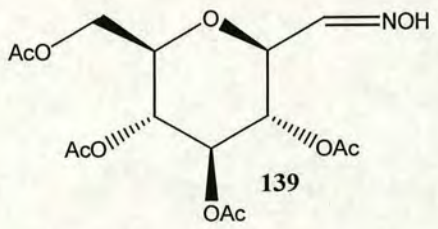
3.2.4 Synthesis of pyranosyl oximes

The D-glucose, D-mannose and L-fucose based oximes (**139**), (**140**), (**138**), (**141**) and (**142**), respectively were generated by reduction of the corresponding protected nitromethanes using a modified procedure of Bartra *et al.*

GENERAL PROCEDURE: Triethylamine (5 equiv.) and thiophenol (4.5 equiv.) were added to a solution of tin(II) chloride (1.5 equiv.) in dry THF (6 cm^3) under nitrogen at 0°C. To the resulting solution was added a solution of protected nitromethyl compound (1 equiv.) and the mixture stirred for 16 hours. After removal of the solvent *in vacuo*, the resulting semi-crystalline residue was washed with hexane to remove excess thiophenol and the product separated by dry-flash chromatography (silica, hexane/ether gradient elution) to afford the target compound.

3.2.4.1 Synthesis of 3, 4, 5, 7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol (3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime) (139)

Sample code: KWB05
Molecular formula: $C_{15}H_{21}NO_{10}$
Molecular weight: 375



139

3,4,5,7-Tetra-*O*-acetyl-β-D-glucopyranosylnitromethane (**127**) (500 mg, 1.28 mmole, 1 equiv.) was added to a cooled (ice-bath) solution of tin(II) chloride (363 mg, 1.92 mmole, 1.5 equiv.), triethylamine (0.9 cm^3, 6.4 mmole, 5 equiv.) and thiophenol (0.61 cm^3, 5.76 mmole, 4.5 equiv.) as outlined in the general procedure above. The product (**139**) was isolated by dry flash chromatography, eluting with ether/hexane (416 mg, 87%). (**139**) was further purified (to remove final traces of thiophenol) by recrystallation from a 60:40 ether/hexane mix. The oxime was obtained as a mixture of *E/Z* isomers in a 4:1 ratio; mp 139-141°C (lit.[134] 155-157 °C); ν_{max}/cm^{-1} (Nujol), 3498 (OH); δ_H (260 MHz, $CDCl_3$) 1.95, 1.97, 2.00, 2.01 (12H, 4 x s, 4 x $COCH_3$), 3.72 (1H, ddd, 6-H), 4.09 (1H, dd, 7a-H), 4.04 (1H, dd, 2-H), 4.22 (1H, dd, 7b-H), 5.07 (1H, dd, 3-H), 5.08 (1H, dd, 5-H), 5.24 (1H, dd, 4-H), 7.30 (1H, d, 1-H), 8.40 (1H, br s, OH); *J*(x-y)/Hz 1-2 6.8, 2-3 9.8, 3-4 9.1, 4-5 9.6, 5-6

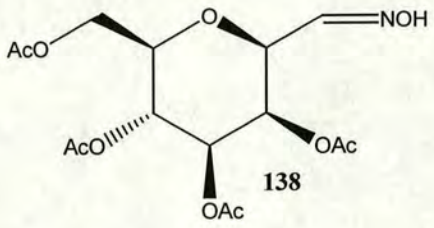
9.6, 6-7a 2.2, 6-7b 4.7, 7a-7b 12.5; δ_C (90 MHz, $CDCl_3$) 20.5, 20.5, 20.6 (4 x $COCH_3$), 61.8 (C-7), 68.0, 69.4, 73.4, 75.6, 75.7 (C-2, C-3, C-4, C-5, C-6), 146.6 (C-1), 169.4, 169.6, 170.2, 170.7 (4 x $COCH_3$); *m/z* (FAB) Found: M+H 376.12452 $C_{15}H_{22}NO_{10}$ requires 376.12437.

3.2.4.2 Synthesis of 3, 4, 5, 7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-hydroxyimino-D-*glycero*-D-*galacto*-heptitol (3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformaldoxime) (138)

Sample code KWB09

Molecular formula: $C_{15}H_{21}NO_{10}$

Molecular weight: 375

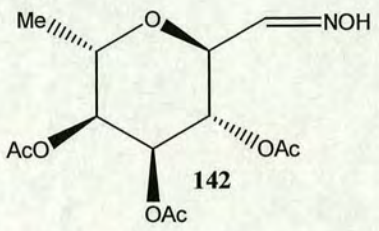


138

3,4,5,7-Tetra-*O*-acetyl-β-D-mannopyranosylnitromethane (**122**) (513 mg, 1.31 mmole, 1.0 equiv.) was added to a cooled solution of tin(II) chloride (371 mg, 2 mmole, 1.5 equiv.), triethylamine (0.9 cm^3, 6.5 mmole, 5 equiv.) and thiophenol (0.61 cm^3, 5.95 mmole, 4.5 equiv.) in THF (6 cm^3) according to the procedure outlined above. The product was isolated by dry flash chromatography, eluting with ether/hexane to yield (**138**) (410 mg, 84%), prepared as a 2.3:1 mixture of *E/Z* isomers; mp 154-156 ° C (from hexane/ether) (lit.[134] 152-154 °C); *E*-isomer: δ_H (360 MHz, $CDCl_3$) 1.96, 2.03, 2.07, 2.13 (12H, s, $COCH_3$), 3.68 (1H, ddd, 6-H), 4.24 (1H, dd, 7a-H), 4.13 (1H, dd, 7b-H), 4.33 (1H, dd, 2-H), 5.08 (1H, dd, 4-H), 5.22 (1H, dd, 5-H), 5.49 (1H, dd, 3-H), 7.30 (1H, d, 1-H), 8.53 (1H, br s, NOH); *J*(x-y)/Hz 1-2 5.5, 2-3 1.1, 3-4 3.3, 4-5 10.1, 5-6 9.8, 6-7a 2.2, 6-7b 5.6, 7a-7b 12.4; δ_C (63 MHz, $CDCl_3$) 20.5, 20.5, 20.6 (4 x $COCH_3$), 62.5 (C-7), 65.5, 69.3, 71.7, 74.5, 76.2 (C-2 – C-6), 146.1 (C-1), 169.6, 170.1, 170.2, 170.8 ($COCH_3$). Selected data for *Z*-isomer: δ_H (360 MHz, $CDCl_3$) 1.95, 2.03, 2.08, 2.11 (12H, s, $COCH_3$), 3.72 (1H, ddd, 6-H), 4.24 (1H, dd, 7a-H), 4.13 (1H, dd, 7b-H), 4.85 (1H, d, 2-H), 5.12 (1H, dd, 4-H), 5.22 (1H, dd, 5-H), 5.81 (1H, dd, 3-H), 6.69 (1H, d, 1-H), 7.79 (1H, br s, NOH); *J*(x-y)/Hz 1-2 4.1, 2-3 1.1, 3-4 3.4, 4-5 10.1, 5-6 9.9, 6-7a 2.2, 6-7b 5.5, 7a-7b 12.4; *m/z* (FAB) Found: M+H 376.12328 $C_{15}H_{22}NO_{10}$ requires 376.12437. The identity of this compound was confirmed by X-ray crystallography (Appendix 1).

3.2.4.3 Synthesis of 3,4,5-tri-*O*-acetyl-2,6-anhydro-1,7-dideoxy-1-hydroxyimino-L-*glycero*-D-*manno*-hepitol (3,4,5-tri-*O*-acetyl-β-L-fucopyranosylformaldoxime) (142)

Sample code: KWB72
Molecular formula: $C_{13}H_{19}O_8$
Molecular weight: 317

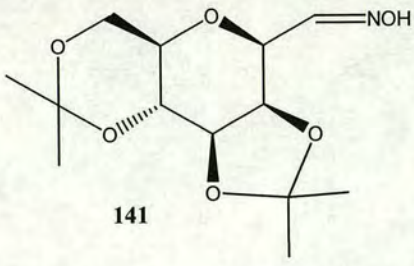


142

Triethylamine (0.2 cm^3, 1.5 mmol) and thiophenol (0.14 cm^3, 1.35 mmol) were added to a solution of tin(II) chloride (100 mg, 0.45 mmol) in dry THF (6 cm^3), followed by tri-*O*-acetyl-β-L-fucopyranosylnitromethane (**129**) (100 mg, 0.3 mmol), as described in the procedure above. The product was isolated by dry-flash chromatography (silica, hexane/ether gradient elution), to afford compound (**142**) (82.6 mg, 90%), as a 7:1 mixture of *E/Z* isomers; mp 37-39 °C; *E*-isomer: $[\alpha]_D^{18}$ -22 (*c* = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.17 (3H, d, 7-H), 1.97, 2.00, 2.17, (9H, 3 x s, $COCH_3$), 3.98 (1H, dd, 2-H), 5.07 (1H, dd, 4-H), 5.13-5.27, (2H, m, 3-H & 5-H), 7.33 (1H, d, 1-H), 8.54 (1H br s, NOH); *J*(x-y)/Hz 1-2 6.9, 2-3 9.7, 3-4 10.2, 4-5 3.3, 5-6 1.0, 6-7 6.4; δ_C (63 MHz, $CDCl_3$) 16.2 (C-7), 20.5, 20.6 ($COCH_3$), 66.8, 70.4, 71.7, 72.9, 75.9 (C-2 – C-6), 147.2 (C-1), 169.9, 170.1, 170.6 ($COCH_3$); *m/z* (FAB): Found M^++1, 318.11880, $C_{13}H_{30}NO_8$ requires 318.11889. The isomer ratio was determined by comparison of the 1-H peaks at 7.33 and 6.75 ppm.

3.2.4.4 Synthesis of 3,4:5,7 di-*O*-isopropylidene-2,6-anhydro-1-deoxy-1-hydroxyimino-D-*glycero*-D-*galacto*-heptitol (3,4:5,7-di-*O*-isopropylidene-β-D-mannopyranosylformaldoxime) (141)

Sample code: KWB108
Molecular formula:$C_{13}H_{21}NO_6$
Molecular weight: 287



141

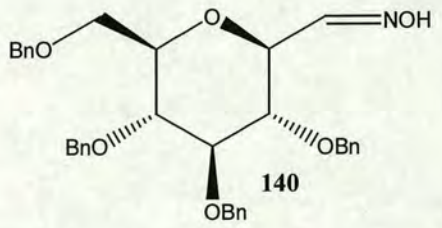
To a mixture of tin(II) chloride (112 mg, 0.50 mmole), thiophenol (1.49 mmole, 0.15 cm^3) and triethylamine (1.65 mmole, 0.23 cm^3) was added 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (100 mg, 0.33 mmole) and the reaction carried out as described in the general procedure above to give the product (**141**) (260 mg, 80%) prepared as a 1.6:1 mixture of *E/Z* isomers; mp 147-148 °C (from hexane/ether); *E*-isomer: δ_H (250 MHz, $CDCl_3$) 1.32, 1.41, 1.40, 1.54 (12H, 4 x s, CH_3), 3.12-3.24 (1H, m, 6-H), 3.70-3.80 (2H, m, 5-H, 7b-H), 3.92 (1H, dd, 7a-H), 4.08 (1H, dd, 4-H), 4.22 (1H, dd, 3-H), 4.40 (1H, dd, 2-H), 7.52 (1H, d, 1-H), 8.49 (1H, br s, NOH); *J*(x-y)/Hz 1-2 6.6, 2-3 2.7, 3-4 5.3, 4-5 7.9, 5-6 nd, 6-7a 5.6, 6-7b 10.0, 7a-7b 10.9; δ_C (63 MHz, $CDCl_3$) 18.6, 26.2, 28.2, 28.8 (4 x CH_3), 61.6 (C-7), 69.6, 72.4, 74.3, 75.2, 75.8 (C-2 – C-6), 99.7, 110.1 (CMe_2), 147.6 (C-1). *Z*-isomer: δ_H (250 MHz, $CDCl_3$) 1.32, 1.41, 1.40, 1.53 (12H, s, 4 x CH_3), 3.12-3.24 (1H, m, 6-H), 3.70-3.80 (2H, m, 5-H, 7b-H), 3.91 (1H, dd, 7a-H), 4.08 (1H, dd, 4-H), 4.57 (1H, dd, 3-H), 5.02 (1H, dd, 2-H), 6.84 (1H, d, 1-H), 8.84 (1H, br s, NOH); *J*(x-y)/Hz 1-2 4.7, 2-3 2.7, 3-4 5.3, 4-5 7.9, 5-6 nd, 6-7a 5.6, 6-7b nd, 7a-7b 10.9; δ_C (63 MHz, $CDCl_3$), 18.6, 26.1, 28.2, 28.8 (4 x CH_3), 61.6 (C-7), 69.3, 70.6, 72.6, 73.2, 75.5 (C-2 – C-6), 99.7, 109.9 (CMe_2), 148.3 (C-1); *m/z* (FAB): Found: M^++1, 288.14549, $C_{13}H_{22}NO_6$ requires 288.14471.

3.2.4.5 Synthesis of 3,4,5,7-tetra-*O*-benzyl-2,6-anhydro-1-deoxy-1-hydroxyimino-D-*glycero*-D-*gulo*-hepitol (3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylformaldoxime) (140)

Sample code: KWB230

Molecular formula: $C_{35}H_{37}NO_6$

Molecular weight: 567



140

To a mixture of tin(II) chloride (220 mg, 1.16 mmole), thiophenol (3.50 mmole, 0.35 cm^3), and triethylamine (3.88 mmole, 0.54 cm^3) was added 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (**131**) (447 mg, 1.16 mmole), and the reaction carried out as described in the procedure above to yield the product (**140**) (284 mg, 65%) prepared as a 4.2:1 mixture of *E/Z* isomers; mp 127-128°C (from hexane/ether); δ_H (250 MHz, $CDCl_3$) 3.53-4.06 (7H, m, 1-H – 7H), 4.55-5.05 (8H, m, $PhCH_2$), 6.85 (0.2H, d, $J_{1,2}$ 7.0 Hz, 1-H *Z*-isomer), 7.18-7.45 (20.8H, m, PhH & 1-H *E*-isomer), 8.42 (0.8H, br s, NOH *E*-isomer), 8.74

(0.2H, br s, NOH *Z*-isomer); δ_C (63 MHz, $CDCl_3$) 68.8 (C-7), 73.7, 75.1, 75.3, 75.9 ($PhCH_2$), 77.0, 77.9, 79.0, 80.0, 86.7 (C-2 – C-6), 128.3, 128.4, 128.8, 128.9 (20 x PhCH), 138.0, 138.3, 138.4, 138.9 (PhC), 148.9 (C-1 *E*-isomer), 149.2 (C-1 *Z*-isomer); *m/z* (FAB): Found: M^++1, 568.26725, $C_{35}H_{37}NO_6$ requires 568.26991.

3.2.5 Synthesis of hydroximoyl chlorides

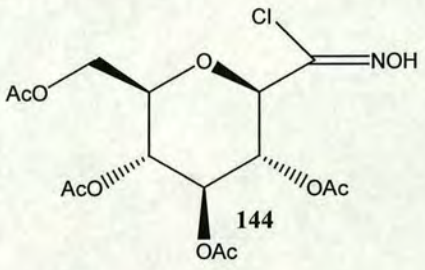
GENERAL PROCEDURE: Dry chlorine gas was bubbled through a solution of the pyranosylformaldoxime (*ca* 1 mmol), in dry dichloromethane (15 cm^3), at -78 °C until the colour changed from blue to green. On warming to room temperature the colour faded and the solvent was removed *in vacuo* to afford an oil. The product was dissolved in *ca* 1 cm^3 of dichloromethane and allowed to crystallise.

3.2.5.1 Synthesis of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol (144)

Sample code: KWB06

Molecular formula: $C_{15}H_{20}NO_{10}$

Molecular weight: 409.5



144

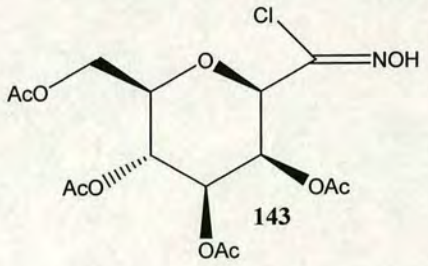
Following the procedure outlined above 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime (**139**) (485 mg, 1.29 mmole) was converted to the hydroximoyl chloride (**144**) as a white solid (500 mg, 95%); mp 157-159 °C (from CH_2Cl_2); υ_{max}/cm^{-1} (Nujol), 3311 (OH), 1747 (C=O); $[\alpha]_D^{18}$ -5.0 (*c* = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.97, 2.00, 2.03, 2.07 (12H, 4 x s, 4 x $COCH_3$), 3.80 (1H, dd, 6-H), 4.14 (1H, dd, 7a-H), 4.23 (1H, dd, 7b-H), 4.31 (1H, d, 2-H), 5.14, 5.26, 5.36 (3H, 3 x dd, 3-H, 4-H, 5-H), 8.93 (1H, br s, NOH); *J*(x-y)/Hz 2-3 9.6, 3-4 nd, 4-5 nd, 5-6 9.8, 6-7a 2.4, 6-7b 4.6, 7a-7b 12.5; δ_C (63 MHz, $CDCl_3$) 20.4, 20.5, 20.5, 20.6 (4 x $COCH_3$), 61.8 (C-7), 67.8, 68.8, 73.7, 75.7, 78.3 (C-2 – C-6), 136.2 (C-1), 169.2, 169.5, 170.5, 170.8 (4 x $COCH_3$); *m/z* (FAB) Found: M^++1, 410.08565. $C_{15}H_{21}NO_{10}{}^{35}Cl$ requires 410.08540; Found: M^++1, 412.08226. $C_{15}H_{21}NO_{10}{}^{37}Cl$ requires 412.08245.

3.2.5.2 Synthesis of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*galacto*- heptitol (143)

Sample code: KWB50

Molecular formula: $C_{15}H_{20}NO_{10}$

Molecular weight: 409.5



143

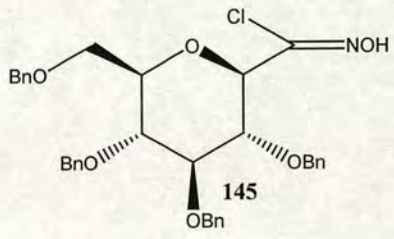
Following the procedure outlined above, 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformaldoxime (**138**) (330 mg, 0.88 mmole) was converted into the hydroximoyl chloride (**143**) (313 mg, 90%), which was in the form of a white powder; mp 102-103 °C; $[\alpha]_D^{18}$ 111.8 (*c* = 0.7, $CHCl_3$); υ_{max}/cm^{-1} (Nujol), 3503 (OH), 1744 (C=O); δ_H (250 MHz, $CDCl_3$) 1.98, 2.04, 2.09, 2.12 (12H, 4 x s, 4 x $COCH_3$), 3.73, (1H, ddd, 6-H), 4.23 (1H, dd, 7a-H), 4.29 (1H, dd, 7b-H), 5.06-5.33 (3H, m, 2-H, 4-H, 5-H), 5.73 (1H, t, 3-H), 8.80 (1H, broad s, NOH); *J*(x-y)/Hz 2-3 1.9, 3-4 3.3, 4-5 nd, 5-6 9.8, 6-7a 2.5, 6-7b 5.6, 7a-7b 12.3; δ_C (90 MHz, $CDCl_3$), 20.38, 20.44, 20.55 (4 x $COCH_3$), 62.4 (C-7), 65.5, 67.7, 71.6, 76.5, 77.1 (C-2 – C-6), 134.6 (C-1), 169.4, 169.5, 169.9, 170.2 (4 x $COCH_3$); *m/z* (FAB) Found: M^++1, 410.08545 $C_{15}H_{21}NO_{10}{}^{35}Cl$ requires 410.08540; Found: M^++1, 412.06859. $C_{15}H_{21}NO_{10}{}^{37}Cl$ requires 412.08245.

3.2.5.3 Synthesis of 3,4,5,7-tetra-*O*-benzyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-hepitol (145)

Sample code: KWB232

Molecular formula:$C_{35}H_{36}ClNO_6$

Molecular weight: 601.5



145

Following the procedure outlined above 3,4,5,7-tetra-*O*-benzoyl-β-D-glucopyranosylformaldoxime (**140**) (146 mg, 0.257 mmole) was converted into the hydroximoyl chloride (**145**) as an oil (122 mg, 82%); δ_H (250 MHz, $CDCl_3$) 3.50-4.12 (7H, m, 1-H – 7H), 4.50-4.81 (8H, m, $PhCH_2$), 7.04 - 7.25 (21H, m, PhH & 1-H), 9.15 (1H, br s, OH); δ_C (63 MHz, $CDCl_3$) 68.8 (C-7). 73.9, 75.4, 75.6, 76.2 (ArCH_2), 78.2, 79.5, 80.2 (C-3

to C-6), 86.6 (C-2), 128.2, 128.4, 128.5, 128.7, 128.9, 130.3 (Ar H), 129.5 (C-1), 138.0, 138.2, 138.3, 138.8 (ArC); *m/z* (FAB) Found: M^++1, 602.23120 $C_{35}H_{37}NO_6{}^{35}Cl$ requires 602.23094; Found: M^++1, 604.22334 $C_{35}H_{37}NO_6{}^{37}Cl$ requires 604.22799

3.3 Nitrile Oxide Cycloadditions: Generation of pyranosylnitrile oxides by dehydration of pyranosylnitromethanes

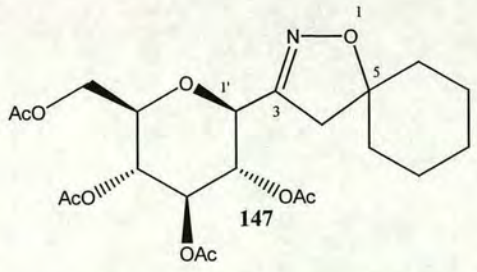
The nitrile oxides were generated from the corresponding protected pyransoylnitromethanes using a modified version of the Mukaiyama procedure, with tolylene diisocyanate (TDI), as the dehydrating agent rather than phenyl isocyante.[9] The general conditions utilised throughout were as outlined below.

GENERAL PROCEDURE: To a solution of the pyranosylnitromethane (0.5 mmole, 1 equiv.) in dry toluene (20 cm^3) under an inert atmosphere (N_2), was added the alkene/alkyne (3 – 5 equiv.), followed by triethylamine (0.1 - 0.2 cm^3) and TDI (3 equiv.) and the mixture heated under reflux for seven days. During this time a polymeric orange solid formed. After cooling to 0 °C 1,2-diaminoethane (3 equiv.) was added dropwise with stirring. After one hour the mixture was filtered through a celite pad to remove the polymeric urea. The pad was washed with toluene (1 x 50 cm^3) and chloroform (2 x 50 cm^3) and the combined organic layers evaporated to afford the product which was purified by chromatography and/or recrystallisation.

3.3.1 Reactions of glucopyranosylnitrile oxides

3.3.1.1 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylformonitrile oxide (115) with methylenecyclohexane *via* the Mukaiyama approach

Sample code:KWB08
Molecular formula:$C_{22}H_{31}NO_6$
Molecular weight: 469



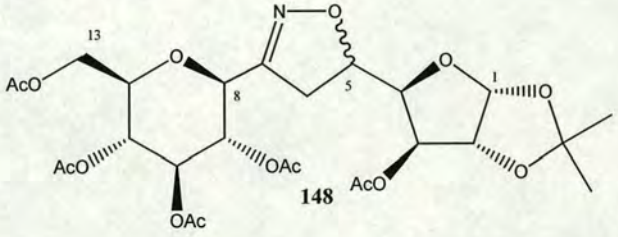
147

Following the procedure outlined above 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylnitromethane (**127**) (200 mg, 0.5 mmole, 1 equiv.) in dry toluene (20 cm^3)

was reacted with methylenecyclohexane (0.3 cm^3, 2.53 mmole, 5 equiv.), triethylamine (cat 0.1 cm^3) and TDI (0.22 cm^3, 1.5 mmole, 3 equiv.). Due to the lower boiling point of the alkene, the reaction was heated to 90°C. 5-(Spirocyclohexyl)-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-isoxazoline (**147**) was isolated by dry flash chromatography eluting from ether/hexane as a white solid (190 mg, 79%), which was recrystallised from ethanol; mp 135-137°C. $[\alpha]_D^{18}$ – 42.0 (*c* = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.22-1.67 (10H, broad m, 6a-H to 10b-H), 1.99, 2.02, 2.06 (12H, 4 x s, 4 x $COCH_3$), 2.68 (1H, d, $J_{4a\text{-}4b}$ 17.1, 4a-H), 2.78 (1H, d, $J_{4b\text{-}4a}$ 17.1, 4b-H), 3.73 (1H, ddd, 5'-H), 4.08 (1H, dd, 6a'-H), 4.21 (1H, dd, 6b'-H), 4.29 (1H, d, 1'-H), 5.04 (2H, t, 2'-H and 4'-H), 5.27 (1H, t, 3-H); *J*(x-y)/Hz 1'-2' 10.0, 2'-3' 9.4, 3'-4' 9.4, 4'-5' 10.0, 5'-6b' 5.1, 5'-6a' 2.2, 6a'-6b' 12.4; δ_C (90 MHz, $CDCl_3$) 20.42, 20.46, 20.49, 20.63 (4 x $COCH_3$), 23.13, 23.26, 24.78, 36.12, 36.42 (C-6 to C-10), 42.19, (C-4), 61.95 (C-6'), 68.18, 68.61, 73.25, 740.25, 75.80 (C-1'to C-5'), 87.46 (C-5), 154.12 (C-3), 169.43, 169.65, 169.93, 170.50 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H, 470.20227 $C_{22}H_{32}NO_{10}$ requires M^++H 470.20262.

3.3.1.2 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylformonitrile oxide (115), with 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (149)

Sample code: KWB16
Molecular formula: $C_{26}H_{35}NO_{15}$
Molecular weight: 601



148

Following the procedure outlined above 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylnitromethane (**127**) (200 mg, 0.5 mmole, 1 equiv.) in dry toluene (20 cm^3), was reacted with 3-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**149**) (supplied by A. R. March) (470 mg, 2 mmole, 4 equiv.), triethylamine (cat 0.1 cm^3) and TDI (0.22 cm^3, 1.5 mmole, 3 equiv.). The product (**148**) was isolated from unreacted alkene (174 mg) by dry flash chromatography eluting from ether/hexane, as a mixture of isomers in a 3:1 ratio (231 mg, 75%). The major isomer was isolated by recrystallisation from ethanol; mp 182-184°C; $[\alpha]_D^{18}$ –114.0 (*c* = 2.65, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 1.22,

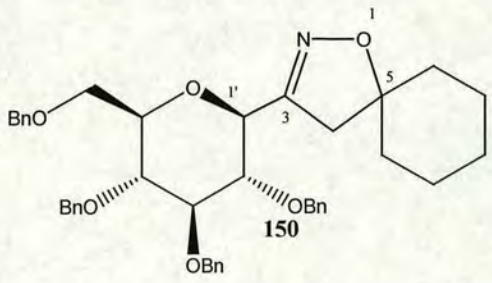
1.42 (6H, 2 x s, C(CH_3)$_2$), 1.93, 1.93, 1.95, 2.00, 2.03 (15H, 5 x s, 5 x COCH_3), 3.08-3.10 (2H, m, 6a-6b), 3.70 (1H, ddd, 12-H), 4.03 (1H, dd, 13a-H), 4.17 (1H, dd, 13b-H), 4.28 (1H, dd, 4-H), 4.44 (1H, d, 8-H), 4.67 (1H, dd, 5-H), 4.97 (1H, dd, 9-H), 5.01 (1H, dd, 11-H), 5.16 (1H, dd, 3-H), 5.23 (1H, dd, 10-H), 5.82 (1H, d, 1-H); *J*(x-y)/Hz 1-2 3.2, 2-3 0.0, 3-4 3.2, 4-5 9.5, 5-6a nd, 5-6b nd, 6a-6b nd, 8-9 10.0, 9-10 9.5, 10-11 9.5, 11-12 10.1, 12-13a 5.1, 12-13b 2.2, 13a-13b 12.4; δ_C (63 MHz, $CDCl_3$) 20.3, 20.4, 20.5 (5 x COCH$_3$), 35.7 (C-6), 61.8 (C-13), 68.1 (C-11), 68.7, (C-9), 73.0 (C-10), 73.5 (C-8), 75.7 (C-3), 75.8 (C-12), 76.9 (C-5), 78.7 (C-4), 84.2 (C-2), 104.7 (C-1), 112.1 (*C*(CH$_3$),), 155.5 (C-7), 169.1, 169.2, 169.7, 170.3 (5 x *C*OCH$_3$); *m/z* (FAB) Found: M^++H, 602.20850. $C_{26}H_{36}NO_{15}$ requires M^++H 602.20863.

3.3.1.3 Cycloaddition of 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylformonitrile oxide (116) with methylenecyclohexane

Sample code: KWB202

Molecular formula: $C_{42}H_{47}NO_6$

Molecular weight 661

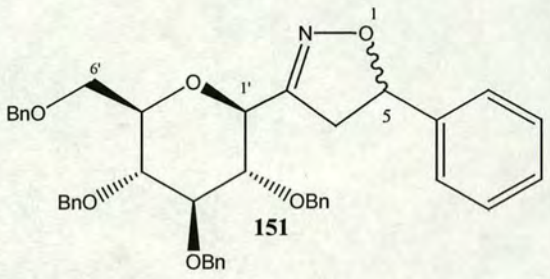


150

Following the general procedure outlined above, 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (**131**) (100 mg, 0.17 mmole) in dry toluene (20 cm^3) was reacted with methylenecyclohexane (0.51 mmole, 3 equiv.), triethylamine (0.1 cm^3) and TDI (0.6 mmole, 3.5 equiv.). After purification by passing as a solution in DCM through a silica pad 5-(spirocyclohexyl)-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-isoxazoline (**150**) was obtained as an oil which solidified on standing (90 mg, 80%); mp = 85 - 87°C; $[\alpha]_D^{18}$ – 11.5 (*c* = 1.82, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.20-1.76 (10H, m, 6-H to 10-H), 2.71 (2 H, dd, 4a-H, 4b-H), 3.45 - 3.88 (6H, m, 2'-H to 6b'-H), 4.21 (1H, d, $J_{1\text{-}2}$ 9.6, 1'-H), 4.57 - 4.99 (8H, m, 4 x ArCH$_2$), 7.18 -7.35 (20H, m, Ar-H); δ_C (63 MHz, $CDCl_3$) 23.2, 23.3, 24.9, 36.2, 36.4 (C-6 to C-10), 43.9 (C-4), 68.6 (C-6'), 73.2, 74.5, 75.0, 75.5 (ArCH$_2$), 75.0, 77.8, 79.0, 79.2, (C-1' to C-5'), 86.6 (C-5),127.5, 127.7, 127.8, 128.0, 128.2, 128.3 (aromatic C-H), 137.7, 137.8, 138.3 (aromatic quat), 155.5 (C-3), *m/z* (FAB) Found: M^++H, 662.34826 $C_{42}H_{48}NO_6$ requires M^++H 662.34816.

3.3.1.4 Cycloaddition of 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylformonitrile oxide (116) with styrene

Sample code: KWB225
Molecular formula: $C_{43}H_{43}NO_6$
Molecular weight: 669



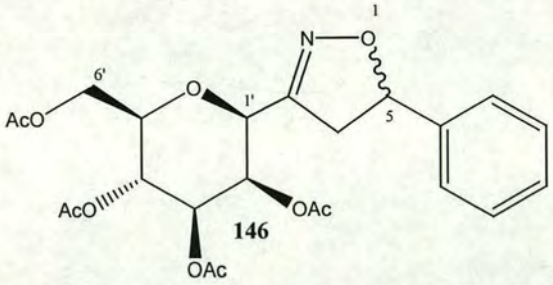
151

Following the general procedure outlined above, 3,4,5,7-tetra-*O*-benzyl-β-D-glucopyranosylnitromethane (**131**) (204 mg, 0.35 mmole), in dry toluene (30 cm^3), was reacted with styrene (1.75 mmole, 5 equiv.), triethylamine (0.2 cm^3), and TDI (1.23 mmole, 3.5 eqiuv.). After purification by passing as a solution in DCM through a silica pad 5(R) and 5(S)-phenyl-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-isoxazoline (**151**) were obtained as an oil which solidified on standing (201 mg, 80%) in a 51:49 ratio as determined by ^{13}C NMR; mp 84 - 86°C; δ_H (250 MHz, $CDCl_3$) major isomer 2.83 (1H, m, 4a-H), 3.40 – 3.70 (7H, m, 4b-H, 2'-H to 6b'-H), 4.22 (1H, d, $J_{1',2'}$ 10.0 Hz, 1'-H), 4.37 – 4.85 (8H, m, 4 x ArCH_2) 7.08 – 7.26 (25H, m, Ph, 4 x *Ar*CH_2); (63 MHz, $CDCl_3$) 66.3 (C-6'), 69.1, 73.8, 74.9, 75.6, 76.2 (ArCH_2), 75.1, 78.4, 78.7, 79.7, 82.4 (C-1' to C-5'), 87.5 (C-5),126.1, 128.1, 128.3, 128.9, 129.1 (aromatic C-H), 138.4, 138.5, 138.3, 141.8 (aromatic quat), 156.2 (C-3); *m/z* Found: M^++H, 670.31741 $C_{42}H_{48}NO_6$ requires M^++H 670.31686.

3.3.2 Reactions of mannopyranosylnitrile oxides

3.3.2.1 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformonitrile oxide (117), with styrene utilising the Mukaiyama approach.

Sample code: KWB25
Molecular formula: $C_{23}H_{27}NO_{10}$
Molecular weight: 477



146

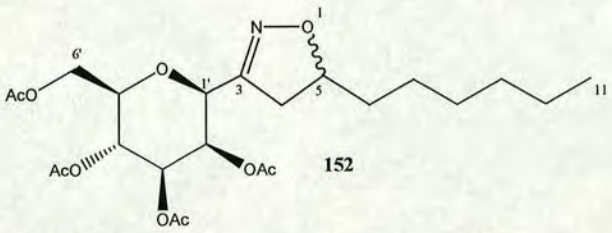
Following the general procedure outlined above, 3,4,5,7-tetra-*O*-β-D-mannopyranosyl nitromethane (**122**) (0.5 mmole, 1 equiv.) in dry toluene was reacted with styrene (0.30 mmole, 5 equiv.), triethylamine (cat 0.1 cm^3) and TDI (1.5 mmole, 3 equiv.). Removal of solvent gave (5R)- and (5S)-5-phenyl-3-(2,3,4,6 tetra-*O*-acetyl-*β*-D-mannopyranosyl)-2-isoxazoline (**146**), as a mixture of inseparable isomers (236 mg, 97%) in a ratio of 56:44; δ_H (250 MHz, $CDCl_3$) 2.02, 2.03, 2.04, 2.05 (12H, 4xs, 4x $COCH_3$), 2.96 (1H, m, 4a-H), 3.44 (1H, m, 4b-H), 3.71, (1H, ddd, 5'-H), 4.14 (1H, dd, 6a'-H), 4.25 (1H, dd, 6b'-H), 4.67, (1H, d, 1'-H), 5.13, (1H, dd, 3'-H), 5.26 (1H, dd, 4'-H), 5.56 (1H, dd, 2-H), 5.51-5.76 (1H, m, 5-H), 7.28 (5H, m, aromatic); *J*(x-y)/Hz 1'-2' 1.3, 2'-3' 3.3, 3'-4' 10.1, 4'-5' 8.9, 5'-6a' 2.2, 5'-6b' 5.8, 6a'-6b' 12.4; δ_C (63 MHz, $CDCl_3$) 20.3, 20.4, 20.5, 20.6 (4x$COCH_3$), 43.2 (C4), 62.4 (C6'), 65.4, 69.9, 71.4, 73.0, 76.6 (C1'to C5'), 81.2 (C5), 125.0, 125.5, 128.5, 128.1, 128.6 (aromatic C-H), 140.8 (aromatic quat), 154.9, (C3), 169.5, 169.8, 169.9, 170.4 (4x $COCH_3$); *m/z* (FAB) Found: 478.317108 $C_{23}H_{28}N_1O_{10}$ requires M^++H 478.17132.

3.3.2.2 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformonitrile oxide (117) with oct-1-ene

Sample code: KWB38

Molecular formula: $C_{23}H_{33}NO_{10}$

Molecular weight: 483



152

Following the general procedure outlined above, 3,4,5,7-tetra-*O*-β-D-mannopyranosyl nitromethane (**122**) (100 mg, 0.256 mmole, 1 equiv.) in dry toluene (10 cm^3) was reacted with oct-1-ene (0.05 cm^3, 0.3 mmole, 1.2 equiv.), triethylamine (0.1 cm^3) and TDI (0.11 cm^3, 0.76 mmole, 3 equiv.). (5R)- and (5S)-hexyl-3-(2,3,4,6- tetra-O-acetyl-β-D-mannopyranosyl)-2-isoxazoline (**152**) was isolated as a clear colourless oil (86 mg, 72%) by passing the oil dissolved in a ether through a silica pad in a ratio of 51:49 determined by ^{13}C NMR; δ_H (250 MHz, $CDCl_3$) major isomer; 0.86 (3H, m, 11-H), 1.24 (10H, m, 6-H to 10-H), 1.94, 2.01, 2.05, 2.05 (12H, 4xs, 4x $COCH_3$), 2.57 (1H, m, 4a-H), 3.00 (1H, m, 4b-H), 3.70, (1H, ddd, 5'-H), 4.11 (1H, dd, 6a'-H), 4.24 (1H, dd, 6b'-H), 4.53 (1H, d, 1'-H), 5.07, (1H, dd,

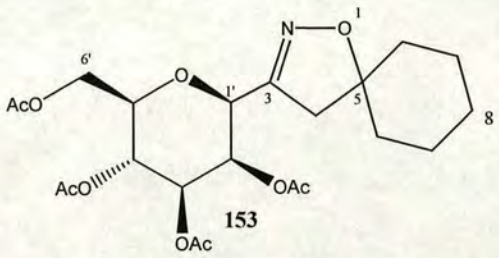
3'-H), 5.23, (1H, dd, 4'-H), 5.56 (1H, dd, 2'-H); *J*(x-y)/Hz 1'-2' 1.2, 2'-3' 3.3, 3'-4' 10.0, 4'-5' 9.3, 5'-6a' 2.4, 5'-6b' 5.9, 6a'-6b' 12.2; δ_C (90 MHz, $CDCl_3$) 13.8, (C-11), 20.4, 20.5, 20.6 (4 x $COCH_3$), 22.3, 25.1, 28.8, 31.4, 34.8 (C-6 to C-10), 39.7 (C-4), 62.5 (C-6'), 65.5, 69.1, 71.6, 73.3, 76.5 (C-1' to C-5'), 80.8 (C-5), 154.6, (C-3), 169.5, 169.8, 169.8, 170.4 (4 x $COCH_3$); *m/z* (FAB) Found M^++H: 484.21788 $C_{23}H_{34}NO_{10}$ requires M^++H 484.21827.

3.3.2.3 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformonitrile oxide (117) with methylenecyclohexane

Sample code: KWB42

Molecular formula: $C_{22}H_{31}NO_{10}$.

Molecular weight: 469



153

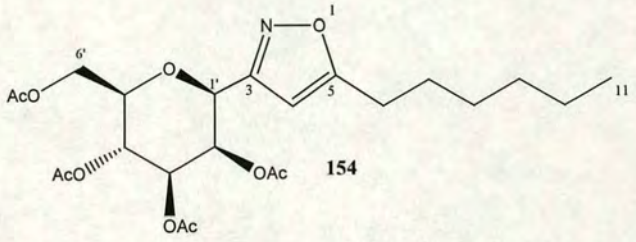
Following the general procedure outlined above, 3,4,5,7-tetra-*O*-β-D-mannopyranosyl nitromethane (**122**) (500 mg, 1.30 mmole, 1 equiv.) in dry toluene (40 cm^3) was reacted with methylenecyclohexane (0.46 cm^3, 3.8 mmole, 3 equiv.), triethylamine (0.3 cm^3) and TDI (0.55 cm^3, 3.8 mmole, 3 equiv.). Removal of solvent *in vacuo* gave a solid which on recrytallisation from ethanol gave 5-(spirocyclohexyl)-3-(2,3,4,6- tetra-O-acetyl-β-D-mannopyranosyl)-2-isoxazoline (**153**) as a white crystalline solid (528 mg, 88%); mp 113-115°C; $[\alpha]_D^{18}$ = -30.0 (*c* = 1 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.22-1.71 (10H, br, m, 6a-H to10-H), 1.97, 2.04, 2.08, 2.12 (12H, 4 x s, 4 x $COCH_3$), 2.64 (1H, d, J_{4a-b} 17.4, 4a-H), 2.73 (1H, d, J_{4a-4b} 17.4, 4b-H), 3.70 (1H, ddd, 5'-H), 4.10 (1H, dd, 6b'-H), 4.26 (1H, dd, 6a'-H), 4.30 (1H, d, 1'-H), 5.09 (1H, 2 x dd, 2'-H, 4'-H), 5.24 (1H, dd, 3'-H); *J*(x-y)/Hz 1'-2' 1.2, 2'-3' 3.3, 3'-4' 10.0, 4'-5' 9.8, 5'-6a' 2.5, 5'-6b' 5.8, 6a'-6b' 12.3; δ_C (63 MHz, $CDCl_3$), 21.0, 21.1, 21.2, 21.2 (4 x $COCH_3$), 23.7, 23.7, 25.3, 36.5, 36.6 (C6 to C10), 45.4 (C-4), 63.2 (C-6'), 66.2, 70.0, 72.2, 74.2, 77.1 (C-1'to C-5'), 87.3 (C-5), 154.9 (C-3), 170.1, 170.1, 170.4, 171.1 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H, 470.20262. $C_{22}H_{31}NO_{10}$ requires M^++H 470.20252.

3.3.2.4 Cycloaddition 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformonitrile oxide (117) with oct-1-yne.

Sample code: KWB47

Molecular formula: $C_{27}H_{33}NO_{10}$

Molecular weight: 483



154

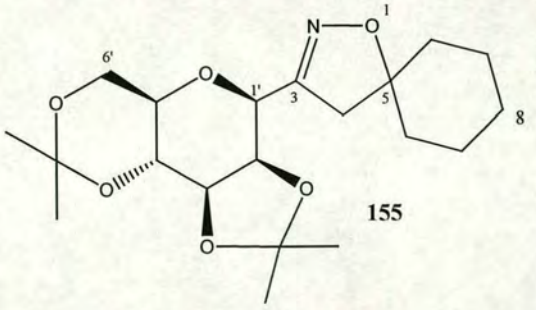
Following the general procedure outlined above, 3,4,5,7-tetra-*O*-β-D-mannopyranosyl nitromethane (**122**) (0.26 mmole, 1 equiv.) in dry toluene (20 cm^3) was reacted with oct-1yne (1.3 mmole, 5 equiv.), triethylamine (0.1 cm^3) and TDI (1.0 mmole, 4 equiv.). Removal of solvent *in vacuo* yielded 5-hexyl-3-(2,3,4,6-tetra-O-acetyl-β-D-mannopyranosyl)isoxazole (**154**) as an oil (120 mg, 88%); δ_H (250 MHz, $CDCl_3$) 0.83 (3H, t, 11-H), 1.25-2.66 (10H, m, 6-H to 10-H), 1.93, 2.01, 2.02, 2.04 (12H, 4 x s, 4 x $COCH_3$), 3.78 (1H, ddd, 5'-H), 4.13 (1H, dd, 6a'-H), 4.26 (1H, dd, 6b'-H), 4.86, (1H, d, 1'-H), 5.16 (1H, dd, 3'-H), 5.28 (1H, dd, 4'-H), 5.60 (1H, dd, 2'-H), 5.97 (1H, s, 4-H); *J*(x-y)/Hz 1'-2' 1.3, 2'-3' 3.3, 3'-4' 10.1, 4'-5' 9.7, 5'-6a' 2.4, 5'-6b' 5.7, 6a'-6b' 12.3; δ_C (90 MHz, $CDCl_3$), 13.8, (C-11), 20.4, 20.4, 20.5, 20.6 (4 x $COCH_3$), 22.2, 26.4, 27.1, 28.4, 31.1 (C-6 to C-10), 62.6 (C-6'), 65.6, 69.4, 71.6, 72.4, 76.5 (C-1' to C-5'), 99.5 (C-4), 159.9, (C-3), 174.0, (C-5), 169.5, 169.8, 170.5 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H, 484.23302 $C_{27}H_{34}NO_7$ requires M^++H 484.23353.

3.3.2.5 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide (118) with methylenecyclohexane

Sample code: KWB94

Molecular formula:$C_{20}H_{32}N_1O_6$

Molecular weight: 381



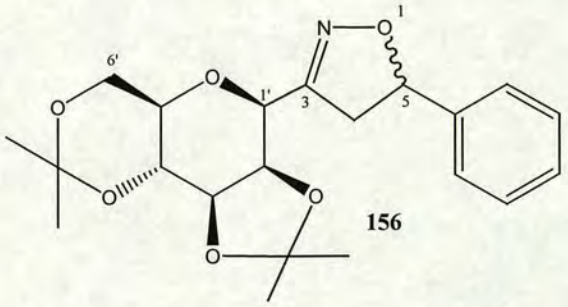
155

Using the usual conditions for the

generation of pyranosyl nitrile oxides *via* Mukaiyama conditions, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (200 mg, 0.66 mmole, 1 equiv.) in sodium-dried toluene (20 cm^3) was reacted with TDI (1.98 mmole, 0.3 cm^3, 3 equiv.), triethylamine (0.1 cm^3, cat) and methylenecyclohexane (2.64 mmole, 0.31 cm^3, 4 equiv.). Purification through a short silica pad eluting with ether yielded 5-(spirocyclohexyl)-3-(2,3;4,7-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-2-isoxazoline (**155**) as a white crystalline solid (210 mg, 84%); mp 160-161°C; δ_H (250 MHz, $CDCl_3$) 1.23- 1.83 (10H, m, 6-H to 10-H), 1.28, 1.39, 1.49, 1.50 (12H, 4 x s, 4 x CC*H*$_3$), 2.80 (2H, 2 x d, 4a-H, 4b-H), 3.17 (1H, ddd, 5'-H), 3.70 (2H, m, 6b'-H. 4'-H), 3.89 (1H, dd, 6a'-H), 4.07 (1H, dd, 3'-H), 4.24 (1H, dd, 2'-H), 4.67 (1H, d, 1-H); *J*(x-y)/Hz 1'-2' 2.7, 2'-3' 5.2, 3'-4' 7.9, 4'-5' 10.1, 5'-6a' 5.7, 5'-6b' 10.0, 6a'-6b' 10.9; δ_C (63 MHz, $CDCl_3$), 18.6, 26.1, 28.2, 28.8 (4 x C*C*H$_3$), 23.2, 23.3, 35.8, 35.9, 36.3 (C-6 to C-10), 44.7 (C-4), 61.6 (C-6'), 69.8, 72.5, 73.0, 75.9, 76.2 (C-1' to C-5'), 86.8 (C-5), 99.5, 109.8 (*C*CH$_3$), 156.6 (C-3); *m/z* (FAB) Found: M^++H, 382.22290 $C_{20}H_{32}NO_6$ requires M^++H 382.22296.

3.3.2.6 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide (118) with styrene

Sample code: KWB111
Molecular formula: $C_{21}H_{27}NO_6$
Molecular weight: 389



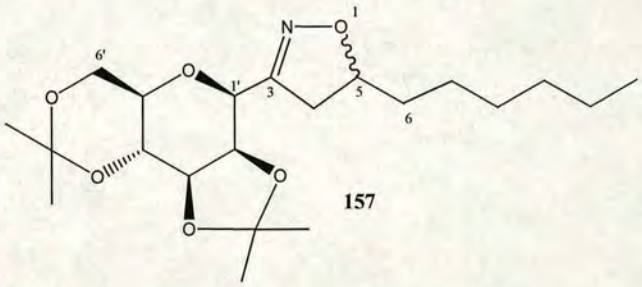
156

Following the general procedure outlined above, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (200 mg, 0.66 mmole), in dry toluene (40 cm^3), was reacted with styrene (0.4 cm^3, 3.3 mmole, 5 equiv.), triethyamine (0.2 cm^3), and TDI (0.28 cm^3, 1.98 mmole, 3 equiv.). 5(R) and 5(S)-phenyl-3-(2,3:4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-2-isoxazoline (**156**) were isolated by dry flash chromatography eluting from ether hexane to give the product as an oil (202 mg, 79%) in a 53:47 ratio, determined by ^{1}H NMR; δ_H (360 MHz, $CDCl_3$) (major isomer) 1.45, 1.53, 1.54, 1.58 (12H, 4 x s, 4 x CC*H*$_3$), 3.12 (1H, dd, 4a-H), 3.26 (1H, m, 5'-H), 3.61 – 3.80 (3H, m, 4'-H, 4b-H, 6b'-H),

3.96 (1H, dd, 6a'-H), 4.15 (1H, dd, 3'-H), 4.33 (1H, dd, 2'-H), 4.84 (1H, d, 1'-H), 5.58 (1H, dd, 5-H), 7.29 – 7.428 (5H, m, Ar H); *J*(x-y)/Hz 1'-2' 2.7, 2'-3' 5.3, 3'-4' 7.9, 4'-5' nd, 5'-6a' 5.6, 5'-6b' nd, 6a'-6b' 10.9, 4a-4b 17.7, 4a-5 8.0, 4b-5 11.1;δ_C (63 MHz, $CDCl_3$)18.6, 26.0, 28.1, 28.7 (4 x C*C*H_3), 42.6 (C-4), 61.5 (C-6'), 69.7, 72.4, 72.7, 75.8, 76.2 (C-1' to C-5'), 82.0 (C-5), 99.5, 109.8 (2 x *C*CH_3), 126.0, 128.0, 128.3 (aromatic C-H), 140.5 (C-6), 156.6 (C-3); minor isomer: δ_H (360 MHz, $CDCl_3$) 1.39, 1.46, 1.55, 1.60 (12H, 4 x s, 4 x C*C*H_3), 3.13 (1H, dd, 4a-H), 3.26 (1H, m, 5'-H), 3.64 (1H, dd, 4b'-H), 3.75 (2H, m 6b'-H, 4'-H), 3.95 (1H, dd, 6a'-H), 4.17 (1H, dd, 3'-H), 4.36 (1H, dd, 2'-H), 4.83 (1H, d, 1'-H), 5.66 (1H, dd, 5-H), 7.29 – 7.428 (5H, m, Ar H);. *J*(x-y)/Hz 1'-2' 2.7, 2'-3' 5.7, 3'-4' 7.9, 4'-5' 10.1, 5'-6a' 5.6, 5'-6b' 10.1, 6a'-6b' 10.9, 4a-4b 17.6, 4a-5 8.3, 4b-5 11.2; *m/z* (FAB) Found: M^++H, 390.19163 $C_{21}H_{28}NO_6$ requires M^++H 390.19166.

3.3.2.7 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide (118) with oct-1-ene

Sample code: KWB125
Molecular formula: $C_{24}H_{35}NO_6$
Molecular weight: 397



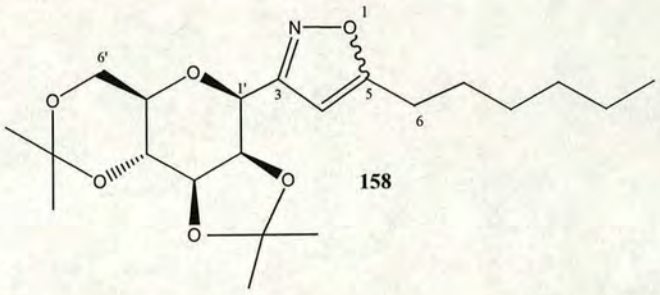
157

Using the general procedure outlined above, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**131**) (100 mg, 0.33 mmole), in dry toluene (20 cm^3), was reacted with oct-1-ene (0.26 cm^3, 1.65 mmole, 5 equiv.), triethylamine (0.1 cm^3), and TDI (0. 14cm^3, 1.0 mmole, 3 equiv.), to give 5(R) and 5(S)-hexyl-3-(2,3;4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-2-isoxazoline (**157**) as a colourless oil (70 mg, 53%) in a 57:43 ratio; δ_H (250 MHz, $CDCl_3$) 0.82 – 1.64 (13H, m, 6-H to 11-H), 1.30, 1.40, 1.50, 1.51 (12H, 4 x s, 4 x C*C*H_3), 2.74 (1H, m, 4a-H), 3.02 - 3.25 (2H, m, 4b-H, 5'-H), 3.63-3.76 (2H, m, 4'-H, 6b'-H), 3.89 (1H, m, 6a'-H), 4.09 (1H, m, 3'-H), 4.22 (1H, m, 2'-H), 4.56 (1H, d, 1'-H), 4.70 (1H, m, 5-H).); *J*(x-y)/Hz 1'-2' 2.6, 2'-3' 5.3, 3'-4' 8.0, 4'-5' 10.0, 5'-6a' 5.6, 5'-6b' 10.0, 6a'-6b' 10.9; δ_C (63 MHz, $CDCl_3$) major isomer 13.9 (C-11), 18.6, 26.2, 28.2, 28.8 (4 x C*C*H_3), 22.4, 25.2, 28.1, 31.5, 34.6 (C-6 to C-10), 39.9 (C-4), 61.6 (C-6'), 69.9, 72.4, 73.6,

75.9, 76.2 (C-1' to C-5'), 99.6, 109.9 (*C*CH_3),156.9 (C-3); *m/z* (FAB) Found: M^++H, 398.25426 $C_{21}H_{36}NO_6$ requires M^++H 398.25426.

3.3.2.8 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide (118) with oct-1-yne

Sample code: KWB162
Molecular formula: $C_{21}H_{33}NO_6$
Molecular weight: 395

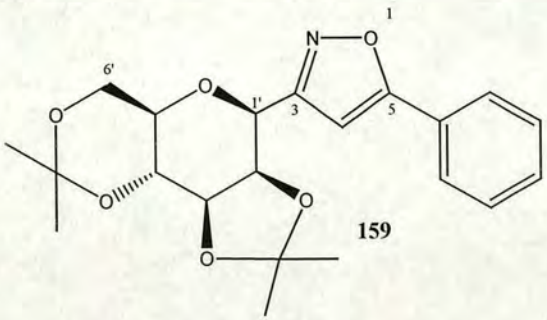


158

Following the general procedure outlined above, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (106 mg, 0.35 mmole), in dry toluene (20 cm^3), was reacted with oct-1-yne (0.26 cm^3, 1.75 mmole, 5 equiv.), triethylamine (0.1 cm^3), and TDI (0.15 cm^3, 1.05 mmole, 3equiv.). 5-Hexyl-(2,3;4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)isoxazole (**158**) was isolated by dry flash chromatography eluting from ether/hexane as an oil (111 mg, 80%); $[\alpha]_D^{18}$ –22.0 (*c* = 1.40, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.82 (3H, t, CH_3), 1.19 – 1.66 (10H, m, 6-H to 10H), 1.25, 1.38, 1.48, 1.50 (12H, 4 x s, 4 x C*C*H_3), 3.26 (1H, m, 5'-H), 3.75 (2H, m, 6a'-H, 6b'-H), 3.88 (1H, dd, 4'-H), 4.10 (1H, dd, 3'-H), 4.31 (1H, dd, 2'-H), 4.92 (1H, d, 1'-H), 6.09 (1H, s, 4-H); *J*(x-y)/Hz 1'-2' 2.3, 2'-3' 5.2, 3'-4' 7.9, 4'-5' 9.9, 5'-6a' 5.7, 5'-6b' 10.1, 6a'-6b' nd; δ_C (63 MHz, $CDCl_3$) 13.9 (C-11), 18.7, 26.2, 28.3, 28.9 (4 x C*C*H_3) 22.3, 26.6, 27.2, 28.6, 31.2 (C-6 to C-10), 61.7 (C-6'), 70.4, 72.1, 72.6, 75.4, 75.9 (C-1' to C-5'), 99.6, 110.0 (*C*$(CH_3)_2$), 100.6 (C-4), 160.7 (C-3), 173.6 (C-5); *m/z* (FAB) Found: M^++H, 396.23922 $C_{21}H_{34}NO_6$ requires M^++H 396.23861.

3.3.2.9 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide (118) with phenylacetylene

Sample code: KWB323
Molecular formula: $C_{21}H_{25}NO_6$
Molecular weight: 387



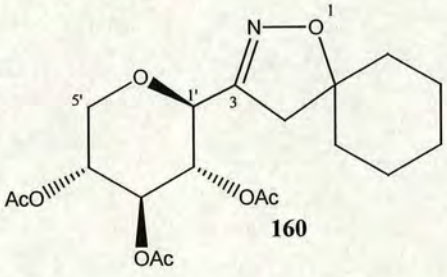
159

Following the general procedure outlined above, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (250 mg, 0.825 mmole) in dry toluene (30 cm^3), was reacted with phenylacetylene (0.45 cm^3, 4.13 mmole, 5 equiv.), triethylamine (0.2 cm^3), and TDI (0.41 cm^3, 2.89 mmole, 3.5 equiv.). 5-phenyl-3-(2,3;4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)isoxazole (**159**) was isolated by dry flash chromatography eluting from ether/hexane (140 mg, 43%); mp = 137-138°C; $[\alpha]_D^{18}$ = -25.0 (*c* = 0.32 in $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.25, 1.48, 1.49, 1.51 (12H, 4 x s, 4 x CCH_3), 3.29 (1H, m, 5'-H), 3.77 - 3.91 (3H, m, 6b'-H, 6a'-H, 4'-H), 4.13 (1H, dd, 3'-H), 4.37 (1H, dd, 2'-H), 5.00 (1H, d, 1'-H), 6.63 (1H, s, 4'-H), 7.19 to 7.74 (5H, m, Ar H); *J*(x-y)/Hz 1'-2' 2.5, 2'-3' 5.2, 3'-4' 7.7, 4'-5' 10.2, 5'-6a' 5.8, 5'-6b' 10.1, 6a'-6b' 10.7; δ_C (63 MHz, $CDCl_3$), 18.7, 26.2, 28.3, 28.9 (4 x CCH_3), 61.7 (C-6'), 70.5, 72.6, 72.1, 75.4, 75.9 (C-1' to C-5'), 99.7, 110.1(CCH_3), 99.5 (C-4), 125.7, 128.8, 130.1 (Ar CH), 127.2 (Ar H), 161.5 (C-3), 169.7 (C-5); *m/z* (FAB) Found: M^++H, 388.17519 $C_{21}H_{26}NO_6$ requires M^++H 388.17601.

3.3.3 Reactions of xylopyranosylnitrile oxides

3.3.3.1 Cycloaddition of 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitrile oxide (116) with methylenecyclohexane

Sample code: KWB133
Molecular formula:$C_{19}H_{27}NO_8$
Molecular weight: 397



160

Using the usual conditions for the generation of pyranosyl nitrile oxides *via* Mukaiyama conditions 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**128**) (250 mg, 0.78 mmole, 1equiv.) in dry toluene (20 cm^3) was heated with TDI (2.35 mmole, 0.33 cm^3, 3 equiv.), triethylamine (0.1 cm^3, cat) and methylene cyclohexane (2.35 mmole, 0.3 cm^3, 3 equiv.). The usual work up yielded a yellow oil which was purified by passing through a short silica pad (ether) to give, on removal of solvent *in vacuo*, 5-(spirocyclohexyl)-3-(2,3,4-tri-*O*-acetyl-*β*-

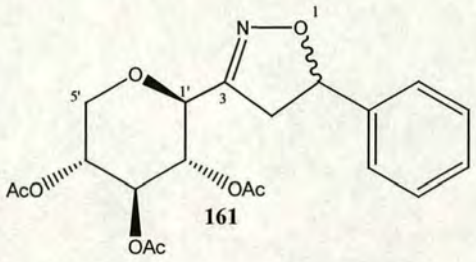
D-xylopyranosyl)-2-isoxazoline as white solid (**160**) (240 mg, 78%); $[\alpha]_D^{18}$ –82.6 (*c* = 0.47, $CHCl_3$); mp 199-200°C; δ_H (250 MHz, $CDCl_3$) 1.24 –1.77 (10H, m, 6-H to 10-H), 2.01, 2.04, 2.04 (9H, 3 x s, 3 x $COCH_3$), 2.73 (2H, 2 x d, $J_{4a,4b}$ 17.2 4a-H, 4b-H), 3.36 (1H, t, 5aq'-H), 4.14 (1H, dd, 5eq'-H), 4.22 (1-H, d, 1'-H), 4.99 (2H, m, 4'-H, 2'-H), 5.28 (1H, dd, 3'-H); *J*(x-y)/Hz 1'-2' 9.9 2'-3' nd, 3'-4' nd, 4'-5ax' 10.7, 4'-5eq' 5.6, 5ax'-5eq' 11.2; δ_C (63 MHz, $CDCl_3$) 20.96, 21.1 (3 x $COCH_3$), 23.7, 25.3, 36.6, 36.9 (C-6 to C-10), 42.8 (C-4) 67.1 (C-5'), 69.3, 69.4, 73.2, 75.5 (C-1' to C-4'), 87.8 (C-5), 154.8 (C-3), 170.2, 170.3, 170.3 (3 x $COCH_3$); *m/z* (FAB) Found: M^++H, 398.18061 $C_{19}H_{28}NO_8$ requires M^++H 398.18149.

3.3.3.2 Cycloaddition of 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitrile oxide (116) with styrene

Sample code: KWB219

Molecular formula: $C_{20}H_{23}NO_8$

Molecular weight: 405



161

Following the general procedure outlined above, 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**128**) (990 mg, 3.1 mmole) in dry toluene (50 cm^3) was reacted with styrene (1.78 cm^3, 15.5 mmole, 5 equiv.), triethylamine (0.3 cm^3) and TDI (1.34 cm^3, 9.3 mmole, 3 equiv.) to give 5(R)- and 5(S)-(spirocyclohexyl)-3-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-2-isoxazoline (**161**) as a white solid (700mg, 60%) in a 55:45 ratio determined by ^{13}C NMR; δ_H (250 MHz, $CDCl_3$) major isomer: 1.96, 1.98, 1.98 (9H, 3 x s, 3 x $COCH_3$), 2.96 (1H, dd, 4a-H), 3.30 (1H, dd, 5a'-H), 3.43 (1H, m, 4b-H), 4.07 (1H, dd, 5b'-H), 4.26 (1H, d, 1'-H), 4.89 – 5.02 (2H, m, 2'-H, 4'-H), 5.25 (1H, dd, 3'-H), 5.48 (1H, t, 5-H), 7.22 – 7.32 (5H, m, ArH); *J*(x-y)/Hz 1'-2' 9.9, 2'-3' 9.5, 3'-4' 9.5, 4'-5ax' 11.0, 4'-5eq' 5.7, 5ax'-5eq' 11.2. 4a-4b 17.3, 4a-5 8.6 4b-5 11.0; δ_C (63 MHz, $CDCl_3$): 20.2, 20.3, 20.7 (3 x $COCH_3$), 40.4 (C-4), 66.3 (C-6'), 68.5, 68.8, 72.2, 74.0, 82.0 (C-1' to C-5'), 125.6, 127.9, 128.3 (aromatic C-H), 140.0 (aromatic quat), 154.9 (C-3), 169.5, 169.6, 169.7 (3 x$COCH_3$); *m/z* (FAB) Found: M^++H, 406.15019 $C_{20}H_{24}NO_8$ requires M^++H 406.15019.

3.4 Nitrile oxide cycloadditions: Generation of pyranosylnitrile oxides from pyranosyl aldoximes

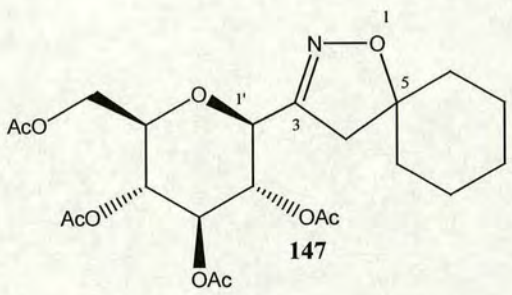
The nitrile oxides were generated by oxidation of their corresponding oximes *in situ* using a modified version of the procedure of Lee *et al.*[19] The general conditions used were as follows:

GENERAL PROCEDURE: Aqueous sodium hypochlorite (5%, 16.2 mmole, 60 equiv.) was added drop-wise to a stirred solution of the pyranosylformaldoxime (0.26 mmole, 1 equiv.) in H_2O/CH_2Cl_2 (1:1, 20 cm^3) with the alkene (5 equiv.). After vigorous stirring overnight the organic layer was separated and the aqueous layer extracted with chloroform (3 x 50 cm^3). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield the product, which was recrystallised from the appropriate solvent

3.4.1 Reactions of glucopyranosylnitrile oxides

3.4.1.1 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-glucopyranosylformonitrile oxide (115), with methylenecyclohexane *via* the hypochlorite method.

Sample code:KWB12
Molecular formula:$C_{22}H_{31}NO_6$
Molecular weight: 469



147

3,4,5,7-tetra-*O*- acetyl-β-D-glucopyranosylaldoxime (**139**) (100 mg, 0.26 mmole, 1 equiv.) and methylenecyclohexane (0.13 cm^3, 1.06 mmole, 4 equiv.) were reacted according to the general procedure above. The product (**147**), was isolated by dry flash chromatography (77 mg, 62%), as was the furoxan (**162**) (60 mg, 30% yield). For analysis see section 3.3.1.1

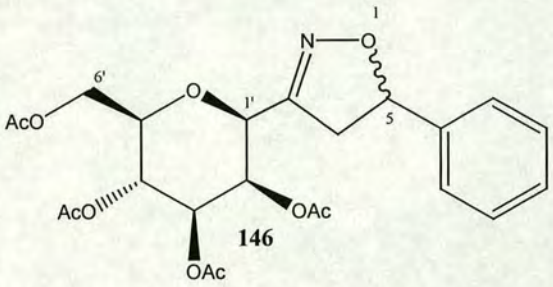
3.4.2 Reactions of mannopyranosylnitrile oxides

3.4.2.1 Cycloaddition of 3,4,5,7-tetra-*O*-acetyl-β-D-mannopyranosylformonitrile oxide(117) with styrene *via* the hypochlorite method.

Sample code: KWB24

Molecular formula: $C_{23}H_{27}NO_{10}$

Molecular weight: 477



146

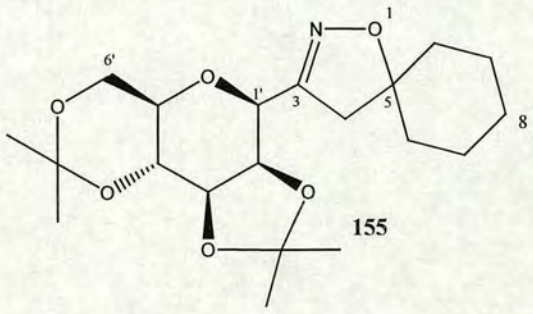
3,4,5,7-tetra-*O*- acetyl-β-D-mannopyranosylnitromethane (**138**) (100 mg, 0.27 mmole, 1 equiv.), and styrene (0.12 cm^3, 1.05 mmole, 4 equiv.) were reacted using the reaction conditions outlined above. (5R)- and (5S)-phenyl-3-(2,3,4,6 tetra-*O*-acetyl-*β*-D-mannopyranosyl)-2-isoxazoline (**146**) was isolated by dry flash chromatography (94 mg, 85%), along with recovered starting material (**138**) (13 mg, 0.04mmole), and a trace of furoxan (**164**). For analysis see section 3.3.2.1.

3.4.2.2 Cycloaddition of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitrile oxide with methylenecyclohexane

Sample code: KWB85

Molecular formula:$C_{20}H_{32}N_1O_6$

Molecular weight: 381



155

2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (60 mg, 0.21 mmole) and methylencyclohexane (0.1 cm^3, 0.84 mmole, 4 equiv.) were reacted using the reaction conditions outlined above. 5-(Spirocyclohexyl)-3-(2,3;4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-2-isoxazoline (**155**) was isolated by dry flash chromatography eluting from ether/hexane to give the product as a white solid (41 mg, 51%). For analysis see section 3.3.2.5.

3.5 Nitrile oxide cycloadditions: Dehydrohaolgenation of pyranosyl hydroximoyl chloride route

The nitrile oxide was generated *in situ* from the hydroximoyl chloride by dehydrochlorination using triethylamine. The general conditions used are outlined below.

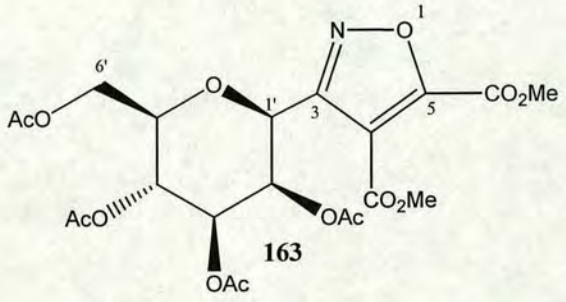
*GENERAL PROCEDURE:*To a solution of the pyransoyl hydroximoyl chloride (0.22 mmole, 1 equiv.) and alkene/alkyne (1.1 mmole, 5 equiv.) in dry ether (10 cm^3), triethylamine (0.25 mmole, 1.1 equiv.) in dry ether (20 cm^3), was added drop-wise *via* syringe pump over a 24 hour period and the solution left to stir for a further 10 hours. The mixture was then poured into water, the organic layer separated and the aqueous layer extracted with chloroform (3 x 50 cm^3). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo*. The product was isolated from by-products by dry flash chromatography eluting from ether/hexane and/or recrystallisation.

3.5.1 Cycloaddition reaction of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile (117) oxide with DMAD

Sample code: KWB30

Molecular formula: $C_{21}H_{25}NO_{14}$

Molecular weight: MW 515



163

Triethylamine (0.04 cm^3, 0.3 mmole) in dry ether (20 cm^3), was added to DMAD (140 mg, 0.98 mmole, 4 equiv.) and the hydroximoyl chloride (**143**) (100 mg, 0.245 mmole, 1 equiv.) in dry ether (20 cm^3), as described in the general procedure above. Dimethyl 3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)isoxazole-4,5-dicarboxylate (**163**) was separated from by-products by dry flash chromatography using ether/hexane elutant. The product was recovered as an oil (89 mg, 70%). Furoxan (**164**) was obtained (14 mg, 15.4%); $[\alpha]_D^{18}$ –35.7 (*c* = 0.84, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 1.97, 2.03, 2.04, 2.05 (12H, 4 x s, 4 x $COCH_3$), 3.82, (1H, ddd, 5'-H), 3.88, 3.95 (6, 2 x s, 2 x $COCH_3$), 4.14 (1H, dd, 6a'-H), 4.24 (1H, dd, 6b'-H), 5.15, (1H, d, 1'-H), 5.20, (1H, dd, 3'-H), 5.28, (1H, dd, 4'-H), 5.78 (1H, dd, 2'-H);

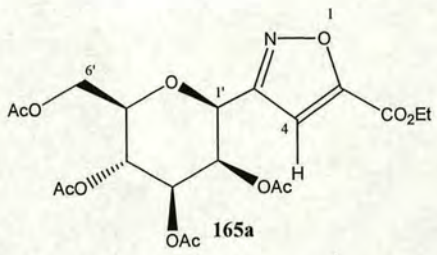
J(x-y)/Hz 1'-2' 1.0, 2'-3' 3.3, 3'-4' 10.0, 4'-5' 9.8, 5'-6a' 2.4, 5'-6b' 5.9, 6a'-6b' 12.4; δ_C (90 MHz, $CDCl_3$) 20.4, 20.5, 20.5, 20.6, (4 x CO_2CH_3), 52.8, 53.4, (2xCH_3), 62.5 (C-6'), 65.7, 67.8, 71.5, 72.1, 77.0 (C-1'to C-5'), 156.1 (C-3), 158.3 (C-5, C-4), 160.0, 160.2 (2 x CO_2CH_3), 169.4, 169.8, 169.9, 170.5 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H, 516.13626. $C_{21}H_{26}NO_{14}$ requires M^++H 516.13533.

3.5.2 Cycloaddition reaction of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117), with ethyl propiolate

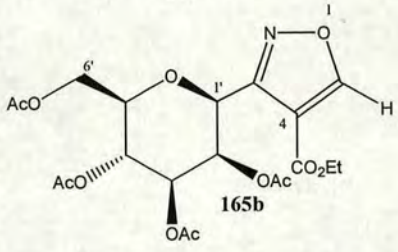
Sample code:KWB23

Molecular formula:$C_{20}H_{25}NO_{12}$

Molecular weight: 472



165a



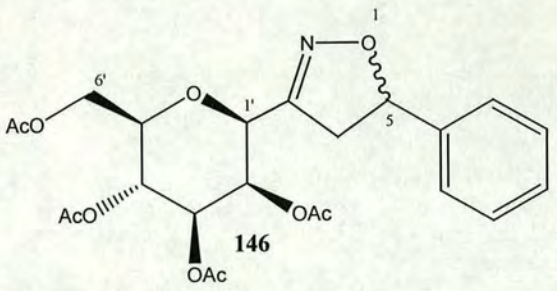
165b

Triethylamine (0.57 cm^3, 0.4 mmole, 1.1 equiv.), was added to ethyl propiolate (158 mg, 1.8 mmole, 5 equiv.), and hydroximoyl chloride (**143**), (150 mg, 0.37 mmole, 1 equiv.), in dry ether (15 cm^3), according to the general procedure above. 3-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-mannopyranosyl)-5-ethylester-isoxazole (**165a**) and 3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-4-ethylester-isoxazole (**165b**) were separated from by-products by dry flash chromatography using ether/hexane elutant as a mixture of two isomers in a 7: 1 ratio (138 mg, 79%). Furoxan (**164**) was obtained (30 mg, 10%); δ_H (250 MHz, $CDCl_3$) for major adduct 1.38 (3H, 1 x t, CH_2CH_3), 1.96, 2.04, 2.05, 2.07 (12H, 4 x s, 4 x $COCH_3$), 3.85, (1H, ddd, 5'-H), 4.16 (1H, dd, 6a'-H), 4.26 (1H, dd, 6b'-H), 4.40, (2H, 1 x q, CH_2CH_3), 4.98, (1H, d, 1'-H), 5.19, (1H, dd, 3'-H), 5.30, (1H, dd, 4'-H), 5.65 (1H, dd, 2'-H), 6.97, (1H, s, 4-H); *J*(x-y)/Hz 1'-2' 1.3, 2'-3' 3.2, 3'-4' 10.1, 4'-5' 9.7, 5'-6a' 2.4, 5'-6b' 5.8, 6a'-6b' 12.3; δ_C (63 MHz, $CDCl_3$), 14.0, (CH_2CH_3), 20.5, 20.6, 20.6 (4 x $COCH_3$), 62.4 (C6'), 65.4, 69.3, 71.5, 72.0, 76.8 (C-1'to C-5'), 108.4 (C-4), 156.3, (C-3), 160.6 (C-5), 160.9 ($COCH_2CH_3$), 169.5,

169.9, 170.5 (4 x *C*OCH$_3$); *m/z* (FAB) Found: M$^+$+H, 472.14599 $C_{20}H_{26}NO_{12}$ requires M$^+$+H 472.14550.

3.5.3 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with styrene

Sample code: KWB27
Molecular formula: $C_{23}H_{27}NO_{10}$
Molecular Weight: 477

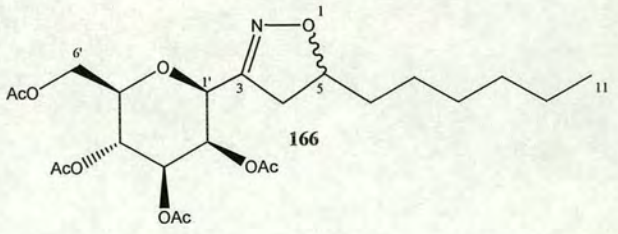


146

Triethylamine (0.07cm^3, 0.05 mmole, 1.4 equiv.), in dry ether (40 cm^3), was reacted with the hydroximoyl chloride (**143**) (133 mg, 0.245 mmole), and styrene (0.2 cm^3, 1.24 mmole, 5 equiv.), in dry ether (15 cm^3), according to the general procedure outlined above. Removal of the solvent *in vacuo* gave (5R)- and (5S)-phenyl-3-(2,3,4,6 tetra-*O*-acetyl-*β*-D-mannopyranosyl)-2-isoxazoline (**146**), as a mixture of inseparable isomers (152 mg, 98% yield) in a ratio of 56:44%. For analysis see section 3.3.2.1

3.5.4 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with oct-1-ene

Sample code: KWB34
Molecular formula: $C_{23}H_{33}NO_{10}$
Molecular weight: 483



166

Triethylamine (0.04 cm^3, 2.88 mmole, 1.2 equiv.), in dry ether (40 cm^3) was reacted with oct-1-ene (4.8 mmole, 20 equiv.), and the hydroximoyl chloride (**143**) (0.24 mmole, 1 equiv.) in dry ether (15 cm^3). (5R)- and (5S)-5-Hexyl-3-(2,3,4,6- tetra-O-acetyl-β-D-

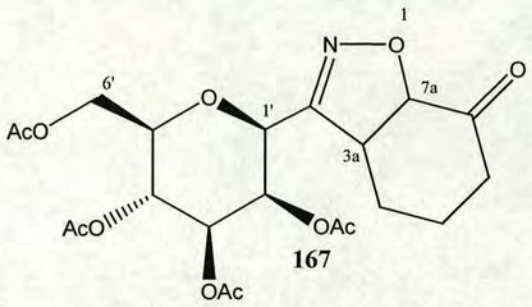
mannopyranosyl)-2-isoxazoline (**166**) were separated from by-products using dry flash chromatography, eluting with ether/hexane (96 mg, 86.6%). Furoxan (**164**) was obtained as a by-product (10 mg, 11.%). For analysis see section 3.3.2.2.

3.5.5 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with cyclohexenone

Sample code: KWB35

Molecular formula: $C_{21}H_{27}NO_{11}$

Molecular weight: 469



167

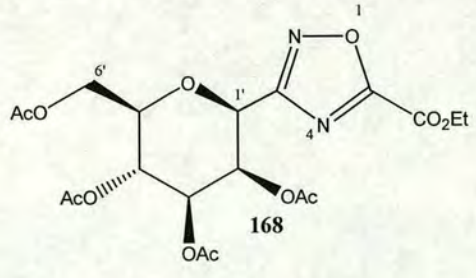
Triethylamine (0.05 cm^3, 0.3 mmole, 1.2 equiv.) in dry ether (40 cm^3), was reacted with cyclohex-2-enone (0.1cm^3, 1 mmole, 4 equiv.) and hydroximoyl chloride (**143**) (105 mg, 0.25 mmole. 1 equiv.) in dry ether (15 cm^3), as outlined in the general procedure above. 3-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-mannopyranosyl)-3a,5,6,7a-tetrahydro-4H-benzo[d]isoxazol-7-one (**167**) was isolated using dry flash chromatography in a (95 mg, 79%). A by-product was detected which was believed to be the nitrile; δ_H (360 MHz, $CDCl_3$) 1.87 (6H, m, 5-H to 7-H), 2.00, 2.05, 2.10, 2.14 (12H, 4 x s, 4 x COC*H*$_3$), 3.75 (1H, d, 3a-H), 3.79, (1H, ddd, 5'-H), 4.14 (1H, dd, 6a'-H), 4.27 (1H, 6b'-H), 4.75, (1H, s, 1'-H), 4.87 (1H, m, 7a-H), 5.14, (1H, dd, 3'-H), 5.29, (1H, dd, 4'-H), 5.66 (1H, dd, 2'-H); *J*(x-y)/Hz 1'-2' 1.0, 2'-3' 3.4, 3'-4' 9.9, 4'-5' 10.0, 5'-6a' 2.2, 5'-6b' 5.4, 6a'-6b' 12.4; δ_C (90 MHz, $CDCl_3$), 21.0, 21.1, 21.1, 21.2 (4 x CO*C*H$_3$),18.5, 26.4, 40.3 (C-5, C-6, C-7), 59.6 (C-7a), 63.0 (C-6'), 66.4, 68.3, 72.1, 74.4, 77.5 (C-1'to C-5'), 81.8 (C-3a), 152.9 (C-3), 170.0, 170.4, 171.0, 171.1 (4 x *C*OCH$_3$), 205.7 (C-8); *m/z* (FAB) Found: M^++H 470.16757 $C_{21}H_{28}NO_{11}$ requires 470.16624.

3.5.6 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with ethyl cyanoformate

Sample code: KWB 26

Molecular formula: $C_{19}H_{24}N_2O_{12}$

Molecular weight: 472

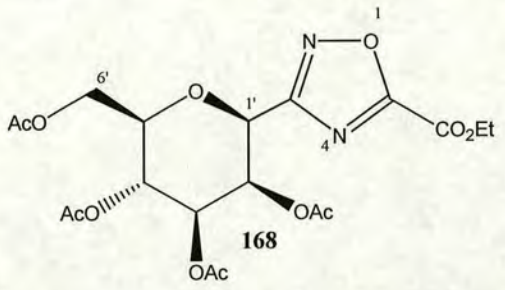


168

Triethylamine (0.05 cm^3, 0.44 mmole, 1.2 equiv.), in dry ether (40 cm^3), was reacted with ethyl cyanoformate (0.18 cm^3, 0.185 mmol, 5 equiv.), and the hydroximoyl chloride (**143**) (125 mg, 0.37 mmole, 1 equiv.) in dry ether (15 cm^3), as described in the general procedure above. The products were isolated using dry flash chromatography eluting with ether/hexane. The 5-ethylester-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-1,2,4-oxadiazole (**168**), was isolated (11 mg, 7%) although trace impurities made full characterisation impossible. The dominant product was the furoxan (**164**) (80 mg 58%) yield.

3.5.7 Cycloaddition 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with ethyl cyanoformate at elevated temperature.

Sample code:KWB36
Molecular formula: $C_{19}H_{24}N_2O_{12}$
Molecular weight: 472



168

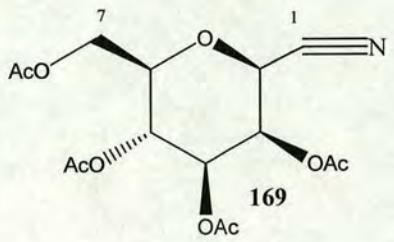
The dipolarophile (0.5 cm^3, 5.22 mmole, 18 equiv.) and hydroximoyl chloride (**143**), (120 mg, 0.29 mmole, 1 equiv.) were dissolved in dry THF and the solution degassed. The system was then heated to 70°C. To this solution triethylamine (0.05 cm^3, 0.35 mmole, 1.2 equiv.), in dry THF was added *via* syringe pump over a 24hr period. The resulting solution was washed with water, the organic layer isolated and the aqueous layer extracted with ether. The organic layer was dried ($MgSO_4$), and the solvent removed *in vacuo*. 5-Ethylester-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-1,2,4-oxadiazole (**168**), was isolated using dry flash chromatography eluting with ether/hexane (20 mg, 14.5%). The major product was the furoxan (**164**) (70 mg, 65%); δ_H (360 MHz, $CDCl_3$), 1.43 (3H, 1 x t, CH_2CH_3), 1.99, 2.06, 2.08, 2.10 (12H, 4 x s, 4 x $COCH_3$), 3.87, (1H, ddd, 5'-H), 4.23 (1H, dd, 6a'-H), 4.33 (1H, dd, 6b'-H), 4.50, (2H, 1 x q, CH_2CH_3), 5.00, (1H, d, 1'-H), 5.20, (1H, dd, 3'-H), 5.36, (1H, dd, 4'-H), 5.77 (1H, dd, 2'-H); *J*(x-y)/Hz 1'-2' 1.0, 2'-3' 3.0, 3'-4' 10.1, 4'-5' 10.3, 5'-6a' 3.0, 5'-6b' 5.5, 6a'-6b' 12.5; δ_C (90 MHz, $CDCl_3$), 14.4, (CH_2CH_3), 21.0 21.1, 21.1, 21.2 (4 x $COCH_3$), 63.0, (CH_2CH_3), 63.0 (C-6'), 64.5, 66.0, 68.5, 72.0, 77.6 (C-1'to C-5'), 154.0, (C-3), 167.4 ($COCH_2CH_3$), 170.0, 170.4, 170.5, 171.1 (4x $COCH_3$); *m/z* (FAB) Found: M^++H, 473.14105 $C_{19}H_{25}N_2O_{12}$ requires M^++H 473.14075.

3.5.8 Cycloaddition 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117), with cyclohexenone at elevated temperature

Sample code: KWB37

Molecular formula: $C_{15}H_{20}NO_9$

Molecular weight: 357



169

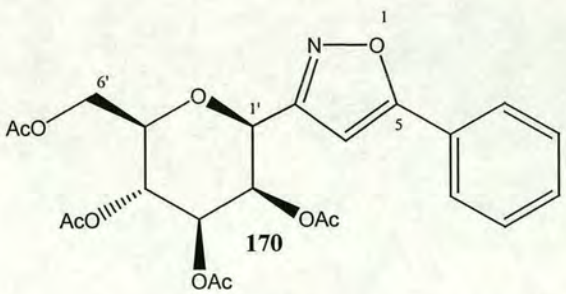
The alkene, (0.2 cm^3, vast excess), and hydroximoyl chloride (**143**) (120 mg, 0.29 mmole, 1 equiv.), were dissolved in dry THF and the solution degassed. The system was then heated to 70°C. To this solution triethylamine (0.05 cm^3, 0.35 mmole, 1.2 equiv.) in dry THF was added *via* syringe pump over a 24hr period. The resulting solution was washed with water, the organic layer isolated and the aqueous layer extracted with ether. The organic layer was dried ($MgSO_4$), and the solvent removed *in vacuo*. The resulting products were isolated by dry flash chromatography. The major product was 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-glycero-D-galacto-heptonitrile (**168**) (60 mg, 58%), with the desired product (**169**) only observed in trace amounts by TLC. Furoxan (**164**) was isolated (28 mg, 25%); δ_H (250 MHz, $CDCl_3$), 1.99, 2.04, 2.10, 2.24 (12H, 4xs, 4x $COCH_3$), 3.68, (1H, ddd, 6-H), 4.14 (1H, dd, 7a-H), 4.24 (1H, dd, 7b-H), 4.56, (1H, d, 2-H), 5.02, (1H, dd, 4-H), 5.24, (1H, dd, 5-H), 5.60 (1H, dd, 3-H); *J*(x-y),/Hz, 2-3 1.5, 3-4 3.4, 4-5 10.0, 5-6 9.8, 6-7a 2.5, 6-7b 5.7, 7a-7b 12.6; δ_C (90 MHz, $CDCl_3$), 20.37, 20.42, 20.48, 20.61 (4 x $COCH_3$), 61.95 (C-7), 64.6, 66.6, 67.4, 70.4, 76.9 (C-2, to C-6), 113.3 (C-1), 169.3, 169.5, 169.8, 170.5 (4 x $COCH_3$).

3.5.9 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117) with phenylacetylene

Sample code:KWB39

Molecular formula: $C_{23}H_{25}NO_{10}$

Molecular weight: 475



170

Triethylamine (0.04 cm^3, 0.294 mmole) in dry ether (10 cm^3) was reacted with phenyl acetylene (0.14 cm^3, 1.225 mmole, 5 equiv.) and the hydroximoyl chloride (**143**) (100 mg,

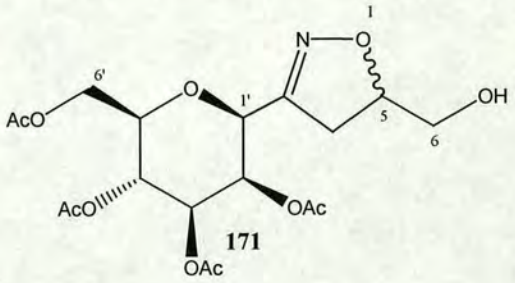
0.245 mmole, 1 equiv.) as described in the general procedure above. 5-Phenyl-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)isoxazole (**170**) was isolated as a white crystalline solid using dry flash chromatography, eluting from ether/hexane (43 mg, 37% yield). Furoxan (**164**) was obtained as a by-product (32 mg, 35%); mp 167-168°C; δ_H (250 MHz, $CDCl_3$) 1.99, 2.06, 2.07, 2.10 (12H, 4 x s, 4 x COC*H*$_3$), 3.85, (1H, ddd, 5'-H), 4.20 (1H, dd, 6a'-H), 4.33 (1H, dd, 6b'-H), 4.96, (1H, d, 1'-H), 5.20, (1H, dd, 3'-H), 5.34, (1H, dd, 4'-H), 5.72 (1H, dd, 2'-H), 6.56, (1H, s, 4-H), 7.60, (5H, m, aromatic); *J*(x-y)/Hz 1'-2' 1.3, 2'-3' 3.3, 3'-4' 9.8, 4'-5' 9.6, 5'-6a' 2.4, 5'-6b' 5.9, 6a'-6b' 12.4; δ_C (90 MHz, $CDCl_3$), 20.5, 20.6, 20.6, 20.7 (4 x $COCH_3$), 62.7 (C-6'), 65.6, 69.4, 71.7, 72.6, 76.7 (C1'to C5'), 98.3 (C-4), 125.7, 128.9, 130.3 (aromatic C-H), 126.9 (aromatic quat), 160.7 (C-3), 169.9 (C-5), 169.6, 169.9, 170.2, 170.6 (4 x $COCH_3$). *m/z* (FAB) Found: M^++H, 476.15621. $C_{23}H_{26}NO_{10}$ requires M^++H 476.15567.

3.5.10 Cycloaddition of 3,4,5,7-tetra-*O*-β-D-mannopyranosylformonitrile oxide (117), with allyl alcohol.

Sample code: KWB53

Molecular fromula: $C_{18}H_{25}NO_{11}$

Molecluar weight: 431



171

Triethylamine (0.03 cm^3, 0.021 mmole), in dry ether (10 cm^3) was reacted with allyl alcohol (0.06 cm^3, 0.88 mmole, 5 equiv.) and hydroximoyl chloride (**143**) (72 mg, 0.176 mmole, 1 equiv.) in dry ether (15 cm^3), TLC of the oil produced showed three products. These were isolated by dry flash chromatography yielding, in order of elution, a unknown product (10mg), probably unreacted oxime (**138**), carried through from the chlorination reaction, the furoxan (**164**), (15 mg, 14 %), and finally the 5-methanol-3-(2,3,4,6-tetra-*O*-acetyl-*β*-D-mannopyranosyl)-2-isoxazoline (**171**), as a white crystalline solid (20 mg, 30%) in a ~ 50:50 ratio, determined by ^{13}C NMR; mp 136-138 °C; δ_H (250 MHz, $CDCl_3$), 1.97, 2.05, 2.08, 2.14 (12H, 4 x s, 4 x COC*H*$_3$), 3.04 (2H, m, 4a-H, 4b-H), 3.47, (1H, m, 6a-H), 3.76 (2H, m, 5'-H, 1b-H), 4.16 (1H, dd, 6a'-H), 4.26 (1H, dd, 6b'-H), 4.60, (1H, d, 1'-H), 4.67 (1H, m, 5-H), 5.11, (1H, dd, 3'-H), 5.25 (1H, dd, 4'H), 5.55 (1H, dd, 2'-H); *J*(x-y)/Hz 1'-2' 1.1, 2'-3' 3.3,

3'-4' 10.1, 4'-5' 9.8, 5'-6a' 2.6, 5'-6b' 5.7, 6a'-6b' 12.4; δ_C (90 MHz, $CDCl_3$), 21.0, 21.1, 21.2 (4 x $COCH_3$), 30.1 (C-6), 36.9 (C-4), 63.1 (C-1), 63.9 (C-6'), 66.1, 69.3 , 70.5, 72.0, 73.8 (C-1' to C-5'), 81.0 (C-5), 156.6 (C-3), 170.1, 170.4, 171.1 (4x $COCH_3$). *m/z* (FAB) Found: M^++H, 432.14988. $C_{18}H_{26}NO_{11}$ requires M^++H 432.15059.

3.6 Dimerisation of pyranosylnitrile oxides to dipyranosyl-1,2,5-oxadiazole-2-oxides (furoxans)

The furoxans were prepared by dimerisation of the corresponding nitrile oxides, which were generated either by dehydration of the pyranosylnitromethane (Method A), or dehydrogenation of the pyranosylformaldoxime (Method B), or dehydrochlorination of the pyranosyl hydroximoyl chloride (Method C).

Method A. To a solution of the pyranosylnitromethane (0.5 mmole, 1 equiv.) in dry toluene (20 cm^3) under nitrogen was added triethylamine (0.1-0.2 cm^3) and tolylene diisocyanate (3 equiv.), and the mixture heated under reflux for seven days. After cooling to 0 °C 1,2-diaminoethane (3 equiv.) was added drop-wise with stirring. After one hour the mixture was filtered through a celite pad to remove the precipitated polymeric urea. The pad was washed with toluene and chloroform and the combined organic layers evaporated to afford the product, which was purified by chromatography and/or recrystallisation.

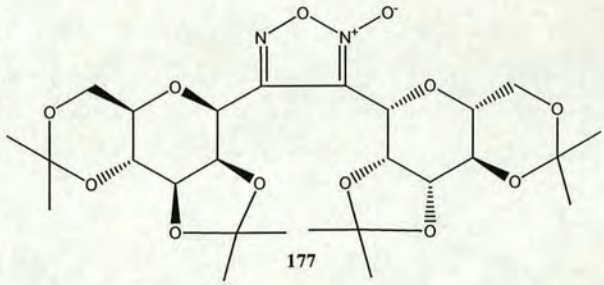
Method B. Aqueous sodium hypochlorite (5%, 16.2 mmole, 60 equiv.) was added drop-wise to a stirred solution of the pyranosylformaldoxime (0.26 mmole, 1 equiv.) in H_2O/CH_2Cl_2 (1:1, 20 cm^3). After stirring overnight the organic layer was separated and the aqueous layer extracted with chloroform (3 x 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the product, which was recrystallised from the appropriate solvent.

Method C. To a solution of the pyransoyl hydroximoyl chloride (0.22 mmole, 1 equiv.) in dry ether (10 cm^3), triethylamine (0.25 mmole, 1.1 equiv.) was added drop-wise *via* a syringe and the solution left to stir overnight. The mixture was then poured into water, the organic layer separated and the aqueous layer extracted with chloroform (3 x 50 cm^3). The combined

organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the product, which was purified by recrystallisation.

3.6.1 Synthesis of 3,4-di(2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (177)

Sample code: KWB80
Molecular formula: $C_{20}H_{39}N_2O_{12}$
Molecular weight: 570



177

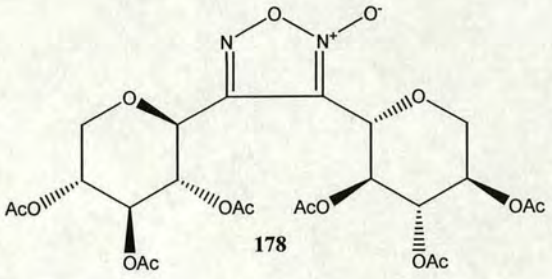
Using the procedure outlined in method A, 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**130**) (220 mg, 0.73 mmole) in dry toluene (20 cm^3) was reacted with triethylamine (0.1 cm^3) and TDI (0.31 cm^3, 2.19 mmole, 3 equiv.) to yield a white solid (**177**) (190 mg, 92%); mp 131-133 °C (from hexane); (Found: C, 54.7; H, 6.8, N, 4.8. $C_{20}H_{38}N_2O_{12}$ requires C, 54.7; H, 6.7, N, 4.9); $[\alpha]_D^{18}$ 29.1 (*c* = 0.23, $CHCl_3$); ν_{max}/cm^{-1} (Nujol) 1606 (C=N); δ_H (600 MHz, $CDCl_3$) 1.35, 1.37, 1.48, 1.48, 1.57, 1.58, 1.58, 1.64 (24H, 8 x s, 8 x C*CH*$_3$), 3.28 (1H, dt, 5"-H), 3.33 (1H, dt, 5'-H), 3.73 (1H, t, 6ax'-H), 3.80 (1H, dd, 4'-H), 3.90 (1H, t, 6ax"-H), 3.97 (dd, 4"-H), 3.99 (1H, dd, 6eq"-H), 4.01 (1H, dd, 6eq'-H), 4.18 (1H, dd, 3"-H), 4.21 (1H, dd, 3'-H), 4.53 (1H, t, 2'-H), 4.54 (1H, t, 2"-H), 5.05 (H, d, 1'-H), 5.21 (1H, d, 1"-H); *J*(x-y)/Hz 1'-2' 2.6, 2'-3' 5.2, 3'-4' 7.9, 4'-5' 10.1, 5'-6ax' 10.7, 5'-6eq' 5.5, 6ax'-6eq' 10.2, 1"-2" 2.4, 2"-3" 5.1, 3"-4" 7.9, 4"-5" 10.1, 5"-6ax" 10.7, 5"-6eq" 5.5, 6ax"-6eq" 10.1; δ_H (600 MHz, CD_3COCD_3) 1.31, 1.32, 1.35, 1.36, 1.52, 1.53, 1.54, 1.56 (24H, 8 x s, 8 x C*CH*$_3$), 3.39 (1H, dt, 5"-H), 3.48 (1H, dt, 5'-H), 3.82 (1H, t, 6ax"-H), 3.85-3.96 (5H, m, 4'-H, 4"-H, 6ax'-H, 6eq'-H, 6eq"-H), 4.19 (1H, dd, 3"-H), 4.28 (1H, dd, 3'-H), 4.64 (1H, dd, 2"-H), 4.68 (1H, dd, 2'-H), 5.31 (H, d, 1'-H), 5.46 (1H, d, 1"-H); *J*(x-y)/Hz 1'-2' 2.7, 2'-3' 5.3, 3'-4' 7.9, 4'-5' 10.0, 5'-6ax' 10.0, 5'-eq' 5.7, 6ax"-6eq" nd, 1"-2" 2.5, 2"-3" 5.2, 3"-4" 7.9, 4"-5" 10.0, 5"-6ax" 10.1, 5"-6eq" 5.7, 6ax"-eq" 10.7; δ_C (63 MHz, $CDCl_3$) 18.7, 18.7, 26.4, 27.3, 28.3, 28.4, 28.7, 28.9 (8 x C*CH*$_3$), 61.5, 61.6, 71.1, 71.4, 72.3, 72.5, 72.6, 73.8, 75.4, 75.8 (C-1' - C-5', C-1" - C-5"), 61.5, 61.6 (C-6', C-6"), 99.9, 100.0, 110.4, 110.5 (4 x *C*CH$_3$), 112.x (C-3), 153.1 (C-4); *m/z* (FAB) Found: M^++1, 571.24946. $C_{20}H_{39}N_2O_{12}$ requires 571.25030.

3.6.2 Synthesis of 3,4-Di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (178).

Sample code: KWB258

Molecular formula: $C_{24}H_{32}N_2O_{16}$

Molecular weight: 602



178

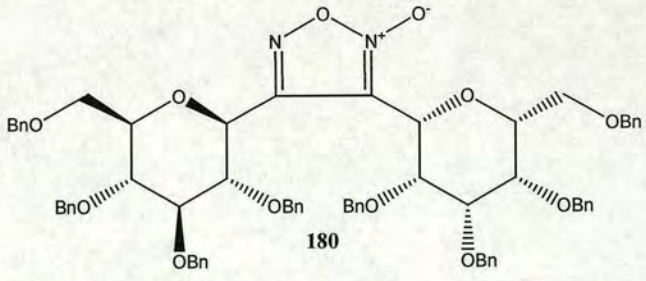
Using the procedure outlined in method A, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl nitromethane (**128**) (1.0 g, 3.13 mmole) in dry toluene (30 cm^3) was reacted with triethylamine (0.5 cm^3) and TDI (1.56 cm^3, 10.97 mmole. 3.5 equiv.) to yield an oil which was purified by dry flash chromatography eluting from ether hexane to give a white solid (**178**) (760 mg, 81%); mp 190 °C; $[\alpha]_D^{18}$ -33 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (Nujol) 1759 (C=O), 1600 (C=N); δ_H (250 MHz, $CDCl_3$) 1.94, 2.03, 2.06, 2.07, 2.07 (18H, 6 x s, 6 x $COCH_3$), 3.40-3.52 (2H, m), 4.10-4.22 (1H, m), 4.29-4.38 (1H, m), 4.62 (2H, 2 x d, $J_{1'-2'}$ 9.5, $J_{1''-2''}$ 9.6, 1'-H, 1"-H), 5.00-5.10 (2H, m), 5.28-5.43 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.0, 20.3, 20.5 (6 x $COCH_3$), 66.9, 66.9 (C-6', C-6"), 68.3, 69.7, 70.2, 71.6, 72.3, 72.4, 73.9, 76.3 (C-1' - C-5', C-1" - C-5"), 112.7 (C-3), 153.7 (C-4), 169.3, 169.5, 169.6, 169.8, 169.9 (6 x $COCH_3$); *m/z* (FAB) 603 (M^++1) 543 [$(M-N_2O_2)^+$+1]; *m/z* (FAB) Found: M^++1, 603.17504. $C_{24}H_{33}N_2O_{16}$ requires 603.17518.

3.6.3 Synthesis of 3,4-Di(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (180)

Sample code: KWB289

Molecular formula: $C_{70}H_{70}N_2O_{12}$

Molecular weight: 1130



180

Using the procedure outlined in method A, 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl nitromethane (**131**) (105 mg, 0.18 mmole) in dry toluene (15 cm^3) was reacted with

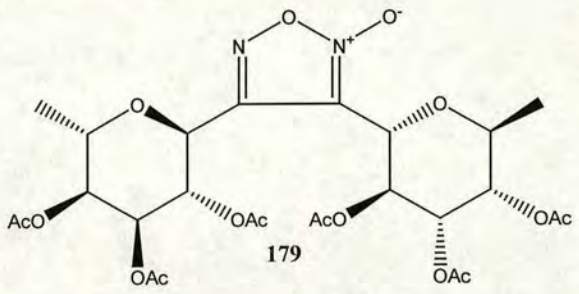
triethylamine (0.1 cm^3) and TDI (0.09 cm^3, 0.63 mmole, 3.5 equiv.) to yield an oil which was purified by dry flash chromatography eluting from ether hexane to give colourless oil (**180**) (56 mg, 55%); $[\alpha]_D^{18}$ –4.9 (*c* = 0.82, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1529 (C=N); δ_H (250 MHz, $CDCl_3$) 3.30 – 3.91 (12H, m, 2'-H to 6'-H, 2''-H to 6''-H), 4.20 – 4.91 (18H, m, $ArCH_2$, 1'-H, 1''-H), 6.97 – 7.32 (40H, m, ArH); δ_C (63 MHz, $CDCl_3$) 68.0, 68.6, 73.4, 74.8, 75.8, 76.0 ($ArCH_2$), 75.2, 75.5, 77.2, 77.6, 77.7, 79.1, 79.3, 79.8, 86.9 (C1'- C5', C1'' – C5''), 114.1 (C3), 127.6, 127.7, 127.8, 128.0, 128.3, 128.6 (ArH), 137.1, 137.3, 137.5, 137.8, 138.0, 138.3 (ArC), 154.9 (C4); *m/z* (FAB) Found: M^++1, 1131.49975. $C_{70}H_{71}N_2O_{12}$ requires 1131.50070.

3.6.4 Synthesis of 3,4-Di(2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl)-1,2,5-oxadiazole 2-oxide (179).

Sample code KWB200

Molecular formula: $C_{26}H_{34}N_2O_{16}$

Molecular weight: 630



179

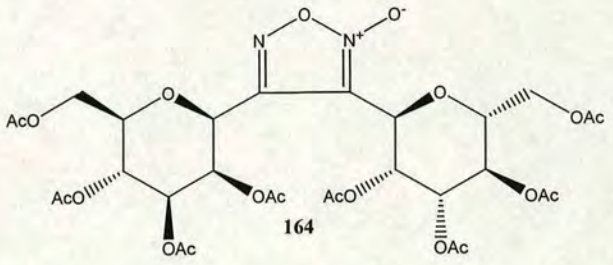
Using the procedure outlined in method A, 2,3,4-tri-*O*-acetyl-β-L-fucopyranosylnitromethane (**129**) (70 mg, 0.2 mmole) in dry toluene (15 cm^3) was reacted with triethylamine (0.1 cm^3) and TDI (0.15 cm^3, 0.7 mmole, 3.5 equiv.) to give an oil which was purified by preparative HPLC (50:50 ethyl acetate / hexane) to give a white solid (50 mg, 79%); mp 212-214 °C (from hexane-EtOAc); $[\alpha]_D^{18}$ 27.8 (*c* = 0.29, $CHCl_3$); δ_H (600 MHz, $(CD_3)_2CO$) 1.20 (3H, d, CH_3'), 1.25 (3H, d, CH_3'') 1.95, 1.95, 1.96, 1.96, 2.22, 2.23(18H, 6 x s, 6 x $COCH_3$), 4.21 (1H, dd, 5'-H), 4.28 (1H, dd, 5''-H), 5.06 (1H, d, 1'-H), 5.11 (1H, d, 1''-H), 5.29 (1H, dd, 3'-H), 5.31 (1H, dd, 3''-H), 5.33 (1H, dd, 3'-H), 5.38 (1H, dd, 4'-H), 5.38 (1H, dd, 4''-H), 5.53 (1H, t, 2'-H), 5.67 (1H, t, 2''-H); *J*(x-y)/Hz 1'-2' 10.1, 2'-3' 1.0, 3'-4' 3.4, 4'-5' 1.0, 5'-6' 6.4, 1"2" 10.1, 2"-3" 1.0, 3"-4" 3.4, 4"-5" 1.0, 5"-6" 6.4; δ_C (63 MHz, $CDCl_3$) 16.7, 16.8 (2 x CH_3), 20.8, 21.0, 21.1, 21.2 (6 x $COCH_3$), 66.4, 67.0, 70.7, 70.7, 71.1, 72.4, 72.7, 72.9, 74.2, 74.3 (C-1' - C-5', C-1" - C-5"), 112.5 (C-3), 153.8 (C-4), 169.7, 170.0, 170.5, 170.6, 170.9, 170.9 (6 x $COCH_3$); *m/z* (FAB) 681 (M^++1), 571 [$(M-N_2O_2)^+$+1]; *m/z* (FAB) Found: M^++1, 631.19732. $C_{26}H_{35}N_2O_{16}$ requires 631.19866.

3.6.5 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (164).

Sample code: KWB11

Molecular formula: $C_{30}H_{38}N_2O_{20}$

Molecular weight: 746



164

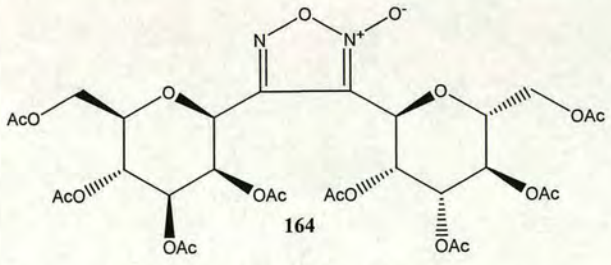
Using the procedure outlined in method B, 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl aldoxime (**138**) (92 mg, 0.24 mmole) was treated with sodium hypochlorite (14.72 mmole, 60 equiv.) to yield the product (**164**) as white needles (28 mg, 32%), mp 213-215 °C (from EtOH) (Found: C, 47.9; H, 5.0, N, 3.8. $C_{30}H_{38}N_2O_{20}$ requires C, 48.2; H, 5.1, N, 3.7); $[\alpha]_D^{18}$ -14.0 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (Nujol) 1743 (C=O), 1606 (C=N); δ_H (250 MHz, $CDCl_3$) 1.93, 1.93, 1.96, 2.02, 2.03, 2.05, 2.05, 2.06, 2.07, 2.11 (24H, 8 x s, 8 x COC*H*$_3$), 3.80-3.94 (2H, m, 5'-H, 5"-H), 4.17-4.36 (4H, m, 6'a-H, 6'b-H, 6"a-H, 6"b-H), 4.93 (1H, d, $J_{1'\text{-}2'}$ 0.9, 1'-H), 5.17 (1H, d, $J_{1"\text{-}2"}$ 1.0, 1"-H) 5.10-5.36 (4H, m, 2'-H, 2"-H, 4'-H, 4"-H) 5.68-5.74 (2H, m, 3'-H, 3"-H); δ_C (63 MHz, $CDCl_3$) 20.3, 20.3, 20.4, 20.4, 20.6, 20.6 (8 x $COCH_3$), 62.1, 62.7 (C-6', C-6"), 64.9, 65.4, 66.0, 67.3, 70.5, 71.0, 71.6, 76.8, 77.1 (C-1', C-2', C-3', C-4', C-5', C-1", C-2", C-3", C-4", C-5"), 110.5 (C-3), 152.7 (C-4), 169.2, 169.3, 169.6, 169.7, 169.9, 170.2, 170.3 (8 x $COCH_3$); *m/z* (FAB) 747 (M^++1), 687 [$(M\text{-}N_2O_2)^+$+1]; *m/z* (FAB) Found: M^++1, 747.20920. $C_{30}H_{39}N_2O_{20}$ requires 747.20962. The structure of compound (**164**) was confirmed by X-ray crystallography.

3.6.6 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (164).

Sample code: KWB20

Molecular formula: $C_{30}H_{38}N_2O_{20}$

Molecular weight: 746



164

Using the procedure outlined in method C, triethylamine (0.035 cm^3) in dry ether (1 cm^3) was added to the hydroximoyl chloride (**143**) (91 mg, 0.22 mmole) in dry ether (1 cm^3) to give the product (**164**) as a white solid (82 mg, 99%). See section 3.5.1 for analysis

3.7 DIOXIME SYNTHESIS

3.7.1 Ring-opening of furoxan ring under hydrogenation conditions

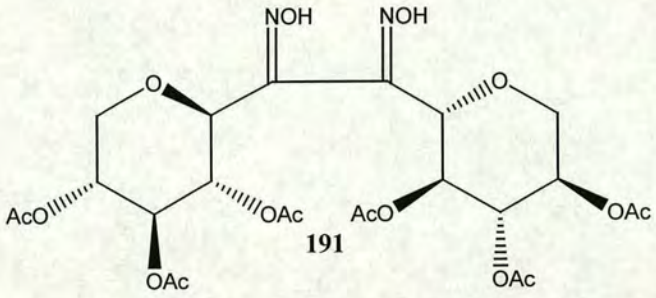
The dioxime (**191**) was synthesised from furoxan (**178**) using the conditions described below using different catalysts

3.7.1.1 Conversion of 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (178) to 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)glyoxime (191) using Pd/C

Sample code: KWB280

Molecular formula: $C_{24}H_{32}N_2O_{16}$

Molecular weight 604



191

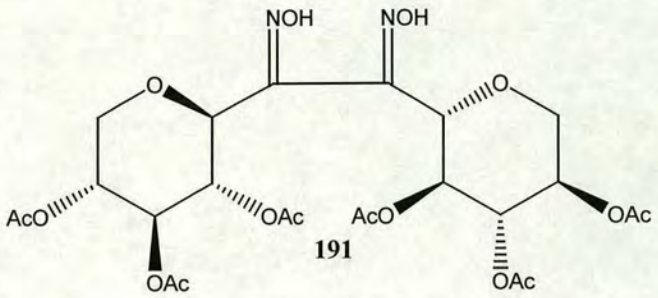
The furoxan (**178**) (280 mg, 0.46 mmole) was dissolved in methanol (10 cm^3) and Pd/C (5%, 100 mg) added. The solution was degassed 3 times and then the reaction mixture was left under an atmosphere of hydrogen for 16 hours. The catalyst was removed by filtration and the solvent removed *in vacuo* to give an orange oil. The product, 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)glyoxime (**191**), was isolated from baseline material by dry flash chromatography, eluting from ether/hexane as a white foam (150 mg, 53%). The product (**191**) appeared to be a mixture of isomers; δ_H (250 MHz, D_3COD) 1.95, 1.96, 2.00 (12H, 3 x s, $COCH_3$), 3.40 (2H, m, 5ax'-H, 5ax''-H), 4.07 (2H, m, 5eq'-H, 5eq''-H), 4.30 (1H, d, 1'-H), 4.91 (2H, m, 4'-H, 4''-H), 4.95 (1H, d, 1''-H), 5.17 (2H, t, 3'-H, 3''-H), 5.35 (2H, t, 2'-H, 2''-H); *J*(x-y)/Hz 1-2 9.9, 2-3 9.0, 3-4 9.8, 4-5ax nd, 4-5eq 5.5, 5ax-5eq 10.9; δ_C (63 MHz, D_3COD) major isomer 22.1, 22.2 (6 x $COCH_3$), 69.0 (C-5', C-5''), 71.5, 71.5, 72.4, 77.1, 80.7, 80.8 (C-1' to C-4' and C-1' to C-4''), 148.7, 151.0 (2 x C=NOH), 172.6, 172.7, 173.0, 173.3, 173.4, 173.4 ($COCH_3$); selected data minor isomer 148.1 (C=NOH).

3.7.1.2 Conversion of 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (178) to 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)glyoxime (191) using Raney nickel

Sample code: KWB300

Molecular formula: $C_{24}H_{32}N_2O_{16}$

Molecular weight 604

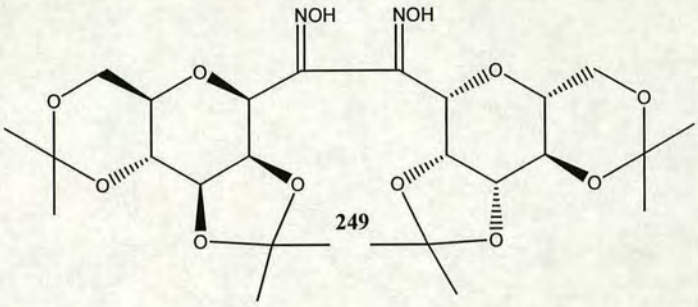


191

The furoxan (**178**) (272 mg, 0.452 mmole) was dissolved in methanol (10 cm^3) and Raney Nickel (6 spatula tips) added. The solution was degassed 3 times and then the reaction mixture was left under an atmosphere of hydrogen for 16 hours. The catalyst was removed by filtration and the solvent removed *in vacuo* to give a red oil. The product (**191**) was isolated by dry flash chromatography as a white solid (211 mg, 77 %) along with a red oil (21 mg); mp 132 – 134°C; $[\alpha]^{18}_D$ –25.0 (c = 0.24, $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 1.93, 1.96, 1.98, 1.98, 2.00, 2.00 (18H, 6 x s, 6 x CO*CH*$_3$), 3.30 (1H, t, 5ax'-H), 3.34 (1H, t, 5ax''-H), 4.11 (1H, dd, 5eq'-H), 4.12 (1H, dd, 5eq''-H), 4.23 (1H, d, 1''-H), 4.93 (1H, m, 4'-H), 4.97 (1H, d, 1'-H), 4.98 (1H, m, 4''-H), 5.17 (1H, t, 3'-H), 5.20 (1H, t, 3''-H), 5.28 (1H, t, 2'-H), 5.40 (1H, t, 2''-H) 9.43, 9.66 (2H, 2 x br s, 2 x OH); *J*(x-y)/Hz 1'-2' 9.9, 2'-3' 9.3, 3'-4' 9.4, 4'-5ax' 10.5, 4'-5eq' 5.7, 5ax'-5eq' 11.4; 1''-2'' 10.0, 2''-3'' 9.5, 3''-4'' 9.4, 4''-5ax'' 10.4, 4''-5eq'' 5.7, 5ax''-5eq'' 11.5; δ_C (63 MHz, $CDCl_3$) 20.5 (6 x CO*C*H$_3$), 66.6 (C-5', C-5''), 68.6, 69.1, 69.6, 71.1, 73.8, 74.1, 77.5 (C-1' to C-4' and C-1' to C-4''), 146.0, 148.6 (2 x C=NOH), 169.9, 170.2, 170.4, 170.5 (*C*OCH$_3$); *m/z* (FAB) Found: M^++H, 605.18256 $C_{24}H_{33}N_2O_{16}$ requires M^++H 605.18301

3.7.1.3 Ring opening of 3,4-di-(2,3:4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-1,2,5-oxadiazole

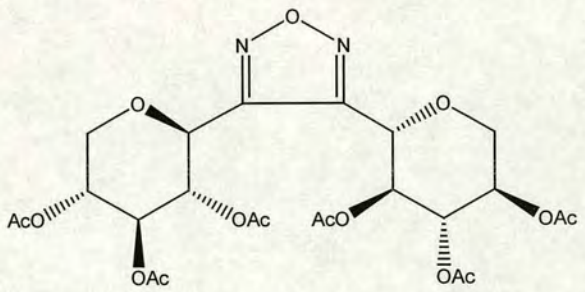
Sample code: KWB275
Molecular formula: $C_{26}H_{40}N_2O_{12}$
Molecular weight: 572



The furoxan (**177**) (90 mg, 0.158 mmole) was dissolved in methanol (10 cm^3) and Pd/C added (5%, 60 mg). The solution was degassed 3 times and then the reaction mixture was left under an atmosphere of hydrogen for 16 hours. The catalyst was removed by filtration and the solvent removed *in vacuo* to give a yellow oil. TLC showed the presence of baseline material which mass spectrum data indicated to be 3,4-di-(2,3:4,6-di-*O*-isopropylidene-*β*-D-mannopyranosyl)-dioxime (**248**) (74 mg, 82%); *m/z* (FAB) Found: M^++H, 573.26727 $C_{26}H_{41}N_2O_{12}$ requires M^++H 573.26565

3.7.2 Dehydration of dioxime (191) to 3,4-di-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole (196)

Sample code: KWB327
Molecular formula: $C_{24}H_{30}N_2O_{15}$
Molecular weight: 586



The dioxime (**191**) (80 mg, 0.132 mmole, 1 equiv.) was dissolved in DCM (3 cm^3) and triethylamine added (0.28 cm^3, 0.200 mmole, 1.5 equiv.). Next DMAP (10 mg, cat.) was added and the solution cooled (ice-bath) and stirred for 30 minutes. Finally acetic anhydride (0.19 cm^3, 1.98 mmole, 15 equiv.) was added and the solution left to stir overnight. The reaction mixture was then diluted with DCM (20 cm^3) the organic layer isolated, washed

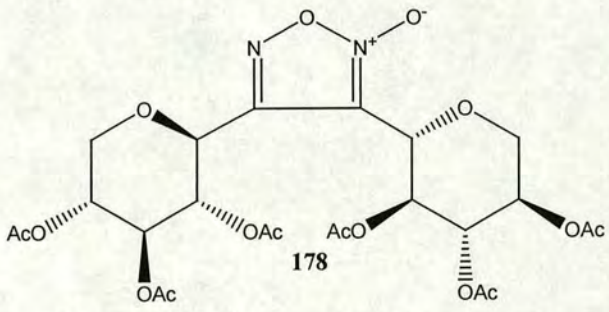
with $NaHCO_3$ (2 x 25 cm^3), water (25 cm^3) and dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil which on purification by dry flash chromatography, eluting from ether / hexane afforded the product (**196**) as a white solid (45 mg, 58%); mp 86 – 88 °C; δ_H (360 MHz, $CDCl_3$) 1.86, 1.98, 2.01 (18 H, 3 x s, 3 x $COCH_3$), 3.43 (2H, m, 5ax'-H, 5ax"-H), 4.28 (2H, dd, 5eq'-H, 5eq"-H), 4.81 (2H, d, 1'-H, 1"-H), 5.04 (2H, m, 4'-H, 4"-H), 5.28 (2H, t, 3'-H, 3"-H), 5.37 (2H, t, 2'-H, 2"-H); *J*(x-y)/Hz 1'-2' 9.7, 2'-3' 9.4, 3'-4' 8.9, 4'-5ax' nd, 4'-5eq' 5.3, 5ax'-5eq' 11.1; δ_C (63 MHz, $CDCl_3$) 20.3, 20.6 (6 x $COCH_3$), 66.9 (C-5', C-5''), 68.5, 70.0, 72.1, 72.7 (C-1' to C-4' and C-1' to C-4''), 150.9 (C=N), 169.2, 169.7, 170.1 (3 x $COCH_3$); *m/z* (FAB) Found: M^++H, 587.17021 $C_{24}H_{31}N_2O_{15}$ requires M^++H 587.17244.

3.7.3 Reoxidation of 3,4-di-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole (196) to3,4-di-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)furoxan (178)

Sample code: KWB328

Molecular formula: $C_{24}H_{30}N_2O_{16}$

Molecular weight: 602



178

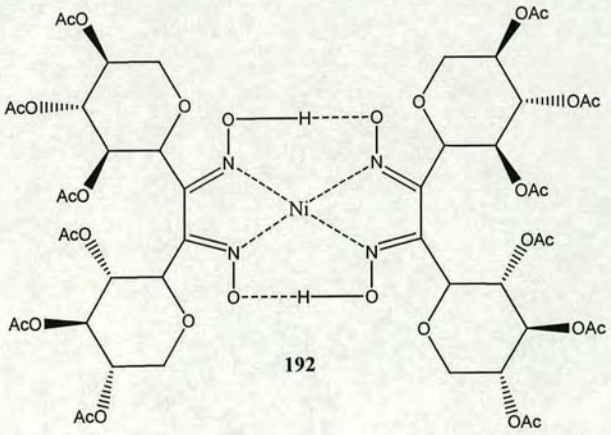
The dioxime (**191**) (75 mg, 0.124 mmole) was dissolved in DCM (2 cm^3) along with triethylamine (cat. 0.1 cm^3). The solution was stirred vigorously and sodium hypochlorite (1 cm^3) added drop-wise over 30 mins. After stirring for 24 hours the solution was diluted with DCM (25 cm^3), washed with water (2 x 25 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the furoxan (**178**) as a white foam (50 mg, 67 %): For analysis see section 3.5.4.

3.7.4 Complexation of 3,4-di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-dioxime (191) with $NiCl_2.6H_2O$

Sample code: KWB343

Molecular formula: $C_{48}H_{62}N_4NiO_{32}$

Molecular weight:1264



192

The dioxime (**191**) (100 mg, 0.166 mmole, 1 equiv.) in ethanol (3 cm^3) was added to a solution of $NiCl_2.6H_2O$ (157 mg, 0.662 mmole, 4 equiv.) in ethanol (3 cm^3) and stirred for 48 hours. A orange solution formed. Removal of solvent *in vacuo* gave an orange solid which was isolated by dissolution in chloroform. Insoluble material was isolated by filtration and the solvent removed *in vacuo* to give a orange solid (**192**) (58 mg, 55%); mp 133-136 °C; δ_H (250 MHz, D_3COD), 1.86, 1.88, 1.92 (12H, 3 x s, $COCH_3$), 3.33 (1H, t, 5ax-H), 4.02 (1H, dd, 5eq-H), 4.21 (1H, d, 1-H), 4.86 (1H, m, 4-H), 5.16 (2H, m, 2'-H, 3'-H); *J*(x-y)/Hz 1-2 9.5, 2-3 9.3, 3-4 9.6, 4-5ax nd, 4-5eq 5.7, 5ax-5eq 10.9 δ_C (63 MHz, D_3COD) 18.7, 18.8, 19.0 ($COCH_3$), 65.7 (C-6', C-6''), 68.2, 68.7, 73.9, 77.0 (C-1' to C-4''), 144.7 (4 x C=NO), 169.4, 169.6, 170.0 ($COCH_3$)

3.8 Deacetylation reactions

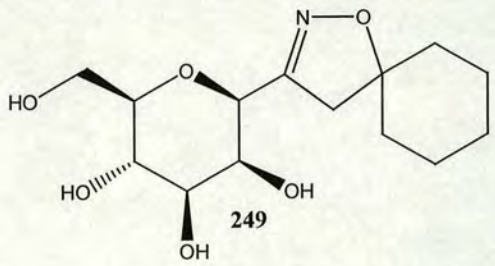
General procedure: The isoxazoline (0.69 mmole) was suspended in methanol (20 cm^3) and then added to a saturated solution of ammonia in methanol (20 cm^3). The reaction was left to stir for 16 hrs and then the solvent was removed *in vacuo* to give the product.

3.8.1 Deacetylation of 5-(spirocyclohexyl)-3-(2,3,4,6- tetra-O-acetyl-β-D-mannopyranosyl)-2-isoxazoline (160)

Sample code: KWB118

Molecular formula: $C_{14}H_{23}NO_6$

Molecular weight: 301



249

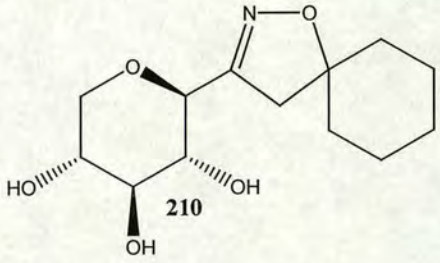
Using the general procedure outlined above, the isoxazoline (**153**) (100mg, 0.21 mmole) was treated with methanol saturated with ammonia. The product (**249**) was isolated by removal of solvent *in vacuo* as a white solid (63 mg, 100%). mp = 137 – 139 °C; δ_H (250MHz, D_2O), 1.49 – 1.77 (10H, m, 6-H to 10-H), 3.00 (2H, d, 4a-H, 4b-H), 3.35 – 3.42 (2H, d, 6a-H, 6b-H), 3.64 (1H, m, 5H), 3.79 (1H, dd, $J_{2,3}$ 6.3, $J_{3,4}$ 12.0. 3-H), 4.05 – 4.47 (2H, m, 2-H, 4-H), 4.46 (1H, d, $J_{1,2}$ 1.0, 1'-H); δ_C (63 MHz, D_2O) 22.6, 24.2, 35.3, (C-6 to C-10) 44.3 (C-4) 61.2 (C-6') 66.5, 70.8, 73.9, 74.5, 80.5 (C-1' to C-5') 85.8 (C-5), 157.8 (C-3). *m/z* (FAB) Found: M^++1, 302.16041 $C_{14}H_{24}NO_6$ requires 302.16036.

3.8.2 Deacetylation of 5-(spirocyclohexyl)-3-(2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl)-2-isoxazoline (160)

Sample code: KWB193

Molecular formula: $C_{13}H_{21}NO_5$

Molecular weight: 271



210

Using the general procedure outlined above, the isoxazoline (**160**) (275 mg, 0.69 mmole) was treated with methanol saturated with ammonia. The product (**210**) was isolated by removal of solvent *in vacuo* as a brown solid (180 mg, 96%); mp 205-206 °C; δ_H (250 MHz, CD_3OD) 1.42 – 1.85 (10H, m, 6-H to 10-H), 2.88 (2H, s, 4a-H, 4b-H), 3.29 – 3.49 (3H, m, 5ax-H, 5eq-H, 1-H), 3.60 (1H, m, 4-H), 3.97 – 4.05 (2H, m, 3-H, 2-H); δ_c (63 MHz, D_2O) 22.4, 22.6, 24.2, 35.3 (C-6 to C-10) 42.3 (C-4) 69.3 (C-5') 69.3, 70.9, 75.7, 77.6, (C-1' to C-4') 86.0 (C-5), 156.8 (C-3); *m/z* (FAB) Found: M^++1, 272.14925 $C_{13}H_{22}NO_5$ requires 272.14980.

3.9 Glycal formation reactions

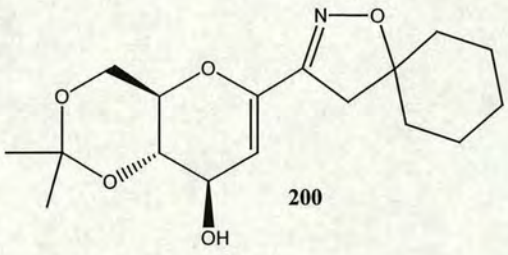
The formation of glycal by elimination of the 2-substituent was induced by treatment with base following the general methods below:

Method 1: Glycals (**200**), (**202**), (**203**), (**204**), (**205**) were formed using the procedure outlined below.

General procedure: THF (5 cm^3) was cooled to -78°C (dry ice / acetone) and n-BuLi (2.5-5 equiv.) was then added drop-wise and the mixture left to stir for 30 minutes. The isoxazoline/isoxazole (1 equiv.) in dry THF (1 cm^3) was then added drop-wise over a 10 minute period and the mixture stirred for a further 2hrs. The reaction was then allowed to warm to room temperature and quenched with saturated NH_4Cl solution. DCM (50 cm^3) was added and the organic layer isolated, the aqueous layer extracted (3 x 50 cm^3), the organic layers combined and dried ($MgSO_4$). The solvent was removed *in vacuo* and product purified by dry flash chromotography and / or recrystallisation.

3.9.1.1 Treatment of 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (155) with BuLi

Sample code: KWB103
Molecular formula: $C_{17}H_{25}NO_5$
Molecular weight 323



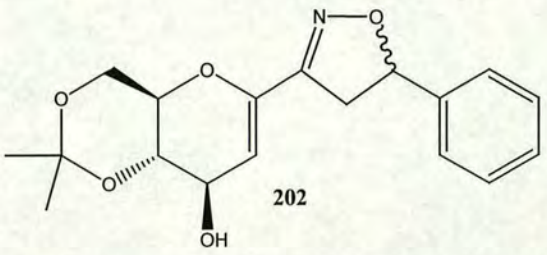
200

Following method 1 above, 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (**155**) (150 mg, 0.40 mmole) in THF (5 cm^3) was treated with butyllithium (0.65 cm^3, 1.0 mmole) to give the 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**200**) (120 mg, 92%) as a white solid (ether/hexane); mp = 69-71 °C; $[\alpha]_D^{18}$ 3.0 (*c* = 1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.23-1.75 (10H, m, 6a-H, 10b-H), 1.43, 1.53 (6H, 2 x s, $C(CH_3)_2$), 2.42

(1H, br. s, OH), 2.76 (2H, d, 4a-H, 4b-H), 3.82 – 3.92 (2H, m, 6a'-H. 6b'-H), 3.96 (1H, m, 4'-H), 4.08 (1H, ddd, 5'-H), 4.45 (1H, m, 3'-H), 5.07 (1H, d, 2'-H); *J*(x-y)/Hz 2'-3' 2.4, 3'-4' 7.9, 4'-5' 5.1, 5'-6a' nd, 5'-6b' 4.5, 6a'-6b' 11.0; δ_C (63Hz, $CDCl_3$) 18.9, 28.8 (C(CH_3)$_2$), 23.2, 23.2, 24.8, 36.1, 36.1 (C6 to C-10) 43.7 (C-4), 61.3 (C-6'), 67.5, 69.5, 72.6 (C-3', C-4', C-5'), 88.0 (C-5), 99.8 (*C*(CH_3)$_2$)$_3$), 106.7 (C-2'), 145.8 (C-1'), 151.6 (C-3); *m/z* (FAB) Found: M^++1, 324.18088 $C_{17}H_{26}NO_5$ requires 324.18110. The structure of (**200**) was confirmed by X-ray crystallography (see Appendix 3).

3.9.1.2 Treatment of 5-phenyl-3-(2,3:4,6-di-*O*-ispropylidine-β-D-mannopyranosyl)-2-isoxazoline (202) with base

Sample code: KWB126
Molecular formula: $C_{18}H_{21}NO_5$
Molecular formula: 331



202

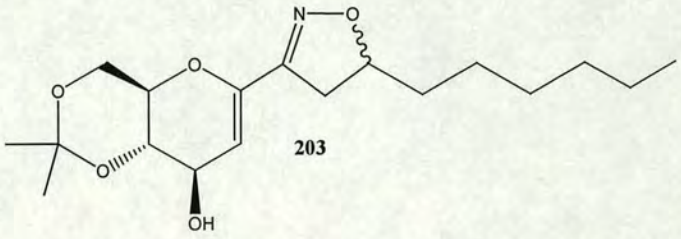
Following method 1 above, 5-phenyl-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (**156**) (100 mg, 0.26 mmole) in THF (5 cm^3) was treated with BuLi (0.4 cm^3, 0.64 mmole, 2.5 equiv.) to give the products, 5(R) and 5(S)-phenyl-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**202**), as a white foam (73 mg, 85%) in a 55:45 ratio; δ_H (250 MHz, $CDCl_3$) 1.44, 1.48 (6H, 2 x s, (C(CH_3)$_2$), 3.04 (1H, dd, 4a-H), 3.51(1H, dd, 4b-H), 3.85-4.04 (3H, m, 4'-H, 6a'-H, 6b'-H), 4.10 (1H, m, 5'-H), 4.44 (1H, dd, 3'-H), 5.12 (1H, d, 2'-H), 5.65 (1H, dd, 5-H); *J*(x-y)/Hz 2'-3' 2.4, 3'-4' 7.5, 4'-5' 5.1, 5'-6a' nd, 5'-6b' 4.7, 6a'-6b' 10.8, 4a-4b 16.6, 4a-5 8.1, 4b-5 11.2; δ_C (63Hz, $CDCl_3$) 18.9, 28.8 (C(*C*H_3)$_2$), 42.1 (C-4), 61.3 (C-6'), 67.3, 69.7, 72.6 (C-3' to C-5') 82.8 (C-5), 99.9 (*C*(CH_3)$_2$), 108.0 (C-2'), 125.6, 128.6 (aromatic C-H), 140.1 (aromatic quat), 145.0 (C-1'), 151.8 (C-3); *m/z* (FAB) Found: M^++1, 332.14951 $C_{18}H_{22}NO_5$ requires 332.14980.

3.9.1.3 Treatment of 5-hexyl-3-(2,3:4,6-di-*O*-ispropylidine-β-D-mannopyranosyl)-2-isoxazoline

Sample code: KWB183

Molecular formula: $C_{18}H_{29}NO_5$

Molecular weight: 339



203

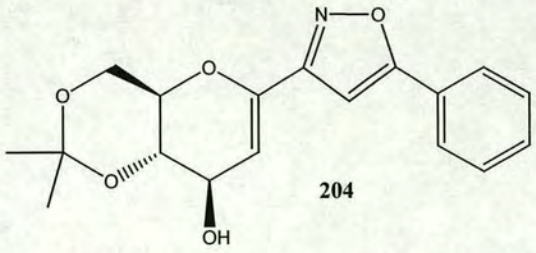
Following method 1 above, 5-hexyl-3-(2,3:4,6-di-*O*-ispropylidine-β-D-mannopyranosyl)-2-isoxazoline (**157**) (130 mg, 0.33 mmole) was treated with BuLi (1 cm^3, 1.63 mmole, 5 equiv.) to give an oil which was purified by dry flash chromatography to give 5(R)-and 5(S)-hexyl-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**203**) as an oil (50 mg, 45%); δ_H (250 MHz, $CDCl_3$) 1.79 (3H, m, 11-H), 1.19 – 1.68 (10H, m, 6-H to 10-H),1.43, 1.53 (6H, 2 x s, $C(CH_3)_2$), 2.51 (1H, br s, OH), 2.68 (1H, dd, 4a-H), 3.11 (1H, m, 4b-H), 3.83 – 3.97 (3H, m, 6a'-H, 6b'-H, 4'-H), 4.08 (1H, m, 5'-H), 4.45 (1H, m, 3'-H), 4.64 (1H, m, 5-H), 5.10 (1H, d, 2-H); *J*(x-y)/Hz 2'-3' 2.3, 3'-4' 7.9, 4'-5' 8.2, 5'-6a' 10.5, 5'-6b' 5.0, 6a'-6b' 10.9, 4a-4b 16.3, 4a-5 7.8, 4b-5 10.6; δ_C (63Hz, $CDCl_3$) 13.9 (C-11) 18.9, 28.8 ($C(CH_3)_2$), 22.4, 25.0, 28.9, 31.5, 34.9 (C-6 to C-10) 38.8 (C-4), 61.3 (C-6'), 67.5, 69.6, 72.6 (C-3' to C-5') 81.9 (C-5), 99.8 ($C(CH_3)_2$), 107.3 (C-2')145.9 (C-1'), 151.8 (C-3); *m/z* (FAB) Found: M^++H, 340.21236 $C_{18}H_{30}NO_5$ requires M^++H 340.21240.

3.9.1.4 Treatment of 5-phenyl-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)isoxazole (159) with base

Sample code: KWB334

Molecular formula: $C_{18}H_{19}NO_5$

Molecular weight: 329



204

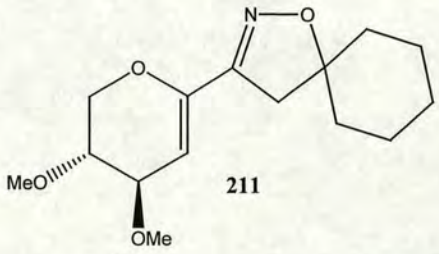
Following method 1 above, 5-phenyl-3-(2,3:4,6-di-*O*-ispropylidine-β-D-mannopyranosyl)isoxazole (60 mg, 0.16 mmole) in THF (5 cm^3) was treated with BuLi (0.3 cm^3, 3 equiv.) to give an oil which was purified by dry flash chromatography to give 5-phenyl-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-isoxazole as a foam (47 mg, 89%); $[\alpha]_D^{18}$ 18.8 (*c* = 0.48, $CHCl_3$); δ_H (250 MHz, $CDCl_3$): 1.41, 1.51 (6H, 2 x s, $C(CH_3)_2$), 2.36 (1H, br s, OH), 3.87 – 3.98 (3H, m , 6a'-H, 6b'-H, 4'-H), 4.06 (1H, m, 5'-H), 4.46 (1H, m, 3'-H), 5.55 (1H, d, 2'-H), 6.53 (1H, s, 4-H), 7.72 - 7.37 (5H, m, aromatic); *J*(x-y)/Hz 2'-3' 2.4, 3'-4' nd, 4'-5' nd, 5'-6a' 10.2, 5'-6b' 5.2, 6a'-6b' nd; δ_C (63Hz, $CDCl_3$) 19.0, 28.8 ($C(CH_3)_2$, 61.4 (C-6'), 67.4, 69.8, 72.8 (C-3' to C-5') 97.1 (C-4) 99.9 ($C(CH_3)_2$), 104.9 (C-2'), 125.7, 128.9, 130.3 (Ar H), 126.9 (Ar C), 144.1 (C-1'), 158.6 (C-3); *m/z* (FAB) Found: M^++H, 330.13420 $C_{18}H_{20}NO_5$ requires M^++H 330.13415.

3.9.1.5 Treatment of 5-(spirocyclohexyl)-3-(2,3,4-tri-*O*-methyl-β-D-xylopyranoysl)-2-isoxazoline (160) with base

Sample code: KWB174

Molecular formula: $C_{15}H_{23}NO_4$

Molecular weight: 281



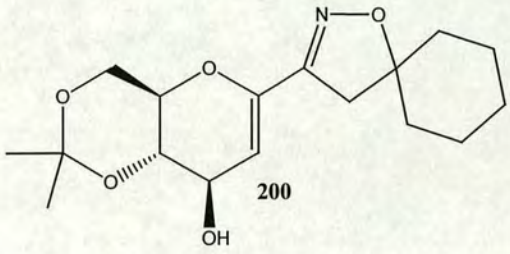
211

Following method 1 above, 5-(spirocyclohexyl)-3-(2,3,4-tri-*O*-methyl-β-D-xylopyranoysl)-2-isoxazoline (**160**) (70 mg, 0.22 mmole) in THF (5 cm^3) was treated with BuLi (0.7 cm^3, 1.12 mmole, 5 equiv.) to give an oil which was purified by dry flash chromatography to give the 5-(spirocyclohexyl)-3-(3,4-di-*O*-methyl-2-deoxy-1,2-didehydro-D-*threo*-pento-pyranosyl)-2-isoxazoline (**211**) (18 mg, 40%) and unreacted starting material (**160**) (20 mg, 0.063 mmole); $[\alpha]_D^{18}$ –103.0 (*c* = 0.54, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 1.24-1.76 (10H, m, H-6a to H-10b), 2.83 (2H, d, 4a-H, 4b-H), 3.47, 3.50 (6H, 2 x s, 2 x OMe), 3.51 (1H, ddd, 4'-H), 3.74 (1H, m, 3'-H), 4.02 (1H, dd, 5eq'-H), 4.33 (1H, ddd, 5ax-H) 5.32 (1H, dd, 2-H); *J*(x-y)/Hz 2'-3' 4.8, 3'-4' nd, 4'-5aq' 5.5, 4'-5eq' 1.9, 5aq'-5eq' 11.9; δ_C (63 MHz, $CDCl_3$) 23.3, 24.8, 36.2 (C-6 to C-10), 43.6 (C-4) 50.1, 56.9 (OMe), 63.3 (C-5'), 71.6, 74.0 (C-3', C-4') 87.8 (C-5), 101.3 (C-2'), 147.4 (C-1'), 152.3 (C-3); *m/z* (FAB) Found: M^++H, 282.17020 $C_{15}H_{24}NO_4$ requires M^++H 282.17053.

Method 2: Glycal (**200**) was formed as described below

3.9.2 Treatment of 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (155) with LDA

Sample code: KWB246
Molecular formula: $C_{17}H_{25}NO_5$
Molecular weight 323



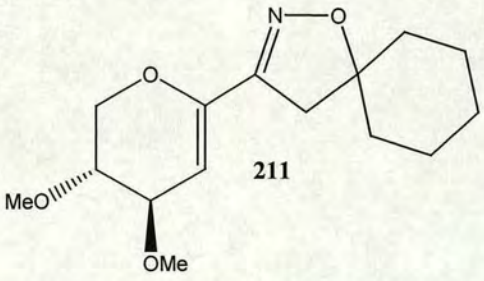
200

Using the same procedure as outlined in method 1, but replacing BuLi with LDA as base, 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (**155**) (177 mg, 0.465 mmole) in THF (10 cm^3) was treated with LDA (0.65 cm^3, 1.16 mmole, 2.5 equiv.) to give 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**200**) (104 mg, 69%) as a white solid (ether/hexane); For analysis see section 3.9.1.

Method 3: Glycal (**211**) was formed as described below

3.9.3 One pot protection and elimination from 5-(spirocyclohexyl)-3-(β-D-xylopyranosyl)-2-isoxazoline (210)

Sample code: KWB305
Molecular formula: $C_{15}H_{23}NO_4$
Molecular weight: 281



211

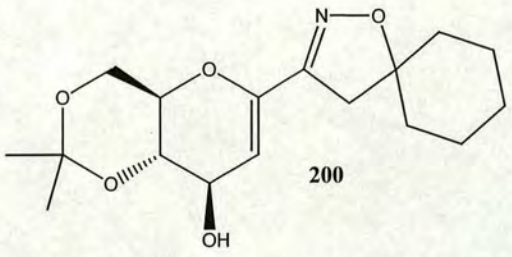
5-(spirocyclohexyl)-3-(β-D-xylopyranosyl)-2-isoxazoline (**210**) (72 mg, 0.26 mmole) was added to a pre-stirred suspension of powdered KOH (0.25 g, 4.25 mmole, 16 equiv.) in

DMSO (3 cm^3) and stirred for 10 minutes. MeI (0.14 cm^3, 2,13 mmole, 8 equiv.) was then added and the reaction mixture stirred for 72 hours. The reaction mixture was extracted with DCM (3 x 50 cm^3), the organic layer washed with brine (2 x 50 cm^3), water (2 x 50 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo.* After purification by dry flash chromatography eluting from ether/hexane, 5-(spirocyclohexyl)-3-(3,4-di-*O*-methyl-2-deoxy-1,2-didehydro-D-*threo*-pento-pyranosyl)-2-isoxazoline (**211**) was isolated as a colourless oil (60 mg, 80%). See section 3.9.1.5 for analysis.

Method 4 Glycal (**200**) was formed as described below

3.9.4 Treatment of 5-(spirocyclohexyl)-3-(2,3:4,6-di-*O*-ispropyl-β-D-mannopyranosyl)-2-isoxazoline (155) with KOH

Sample code: KWB313
Molecular formula: $C_{17}H_{25}NO_5$
Molecular weight 323



200

The isoxazoline (**155**) (200 mg, 0.53 mmole) was added to a pre-stirred suspension of powdered KOH (119 mg, 2.12 mmole, 4 equiv.) in DMSO (5 cm^3) and the reaction mixture stirred for 24 hrs. The reaction mixture was extracted with DCM (3 x 50 cm^3), the organic layer washed with brine (2 x 50 cm^3), water (2 x 50 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. 5-(Spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**200**) was isolated by dry flash chromatography eluting from ether/hexane (100 mg, 59%). For analysis see section 3.9.1.1.

3.10 Glycal manipulations

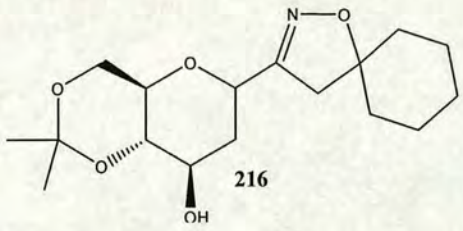
3.10.1 Reduction of the glycal double bong under hydrogenation conditions

Reduction of glycals (**200**) and (**211**) to give the unsaturated products (**216**) and (**217**) was achieved using hydrogenation according to the procedure outlined below:

General procedure: The glycal (0.4 mmole) was dissolved in a 1:1 ethyl acetate / ethanol mix (8 cm^3) and 5% Pd/C added (30 mg). The solution was degassed 3 times and the mixture left stirring under an atmosphere of hydrogen for 16 hours. Insoluble material was removed by filtration and the filtrate was evaporated to give an oil which was purified by dry flash chromatography eluting from ether / hexane.

3.10.1.1 Hydrogenation of 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (200)

Sample code: KWB315
Molecular formula: $C_{17}H_{27}NO_5$
Molecular weight: 325



216

The glycal (**200**) (100 mg, 0.322 mmole) was dissolved in ethylacetate (4 cm^3) and ethanol (4 cm^3) and treated as described in the general procedure above. The product, 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-β-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**216**), along with an unidentified by-product (14 mg) (gave positive test with ninhydrin), was isolated by dry flash chromatography as a white solid (65 mg, 62%); $[\alpha]^{18}_D$ – 10.0 (*c* = 0.8, $CHCl_3$); mp 115-116 °C; δ_H (360 MHz, $CDCl_3$) 1.22 – 1.82 (10H, m, 6-H to 10-H), 1.41, 1.50 (6H, 2 x s, $C(CH_3)_2$), 1.78 (1H, m, 2a'-H), 2.23 (1H, ddd, 2e'-H), 2.59 (1H, br s, OH), 2.70 (2H, q, 4a-H, 4b-H), 3.26 (1H, ddd, 5'-H), 3.46 (1H, t, 4'-H), 3.71 (1H, t, 6b-H), 3.81 (1H, ddd, 3'-H), 3.87 (1H, dd, 6a'-H), 4.37 (1H, dd, 1'-H); *J(x,y)*/Hz 1'-2a' 11.9, 1'-2e' 2.4, 2a'-3' 11.1, 2e'-3' 5.1, 3'-4' 8.8, 4'-5' 9.3, 5'-6a' 5.4, 5'-6b' 10.2, 6a'-6b' 10.7; δ_C (90 MHz, $CDCl_3$) 19.0, 28.9 ($C(CH_3)_2$) 23.2, 36.1, 36.2 (C-6 to C-10), 24.8 (C-2'), 43.5

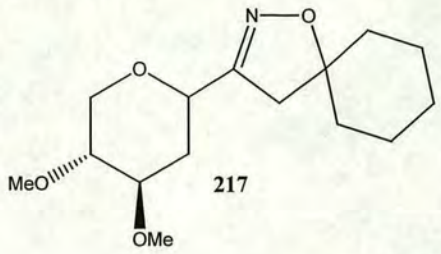
(C-4), 61.9 (C-6'), 69.1, 71.5, 72.0, 75.6 (C-1', C-3' to C-5'), 86.7 (C-5), 99.7 ($C(CH_3)_2$), 157.2 (C-3); *m/z* (FAB) Found: M^++H, 326.19755 $C_{17}H_{28}NO_5$ requires M^++H 326.19675.

3.10.1.2 Hydrogenation of 5-(spirocyclohexyl)-3-(3,4-di-*O*-methyl-2-deoxy-β-D-*threo*-pento-pyranosyl)-2-isoxazoline (211)

Sample code: KWB339

Molecular formula: $C_{15}H_{23}NO_4$

Molecular weight: 283



217

The glycal (**211**) (120 mg, 0.43 mmole), was dissolved in ethylacetate (4 cm^3) and ethanol (4 cm^3) and treated as described in the general procedure above. The product (**217**), along with an unidentified by-product (30 mg) (gave positive test with ninhydrin), was isolated by dry flash chromatography as a colourless oil (68 mg, 56 %); $[\alpha]^{18}_D$ –26.5 (*c* = 1.36, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.34 – 1.66 (10H, m, 6-H to 10-H), 1.50 (1H, m, 2ax'-H), 2.26 (1H, ddd, $J_{1,2eq}$ 2.1, $J_{2eq,3}$ 4.9 2eq'-H), 2.65 (2H, s, 4a-H, 4b-H), 3.10 (3H, m, 4'-H, 5ax'-H, 5eq'-H), 3.22 (1H, m, 3'-H), 3.38 (6H, 2 x s, OMe), 4.09 (1H, m, 1'-H); δ_C (90 MHz, $CDCl_3$) 23.2, 33.4, 36.1 (C-6 to C-10), 24.8 (C-2'), 43.5 (C-4), 56.8, 58.6 (2 x OCH_3), 67.7 (C-5'), 72.2, 79.2, 80.4(C-1'to C-4'), 86.6 (C-5), 157.7 (C-3); *m/z* (FAB) Found: M^++H, 284.18557 $C_{20}H_{32}NO_6$ requires M^++H 284.18616.

3.10.2 Attempted hydroboration of 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (200)

To a stirred solution of the glycal (**200**) (116 mg, 0.36 mmole, 1 equiv.) in dry THF (6 cm^3) was added borane-tetrahydofuran complex (0.72 cm^3, 0.72 mmole, 2 equiv.) in a drop-wise fashion. The mixture was stirred at 0°C for 4 hours and then treated with NaOH (0.24 cm^3, 0.72 mmole, 2 equiv.) and H_2O_2 (0.24 cm^3, 30% w/w). The biphasic mixture was allowed to

warm to room temperature and stirred vigorously for an hour. The resulting solution was extracted with ether (3 x 20 cm^3), the organic portion washed with NH_4Cl (20 cm^3) and brine (20 cm^3) and dried ($MgSO_4$). Removal of solvent *in vacuo* yielded a white foam (100 mg) which was identified as starting material (**200**).

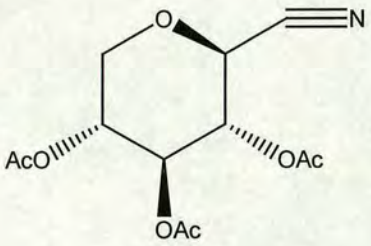
3.10.3 Attempted 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (200)

To a solution of the glycal (**200**) (80 mg, 0.26 mmole, 1 equiv.) in THF (4 cm^3) and t-BuOH (4 cm^3) were sequentially added pyridine (1 cm^3), water (2 cm^3), NMNO (837 mg, 6.2 mmole, 23 equiv.) and OsO_4 (0.01 cm^3). The mixture was heated to reflux for 1 hour, cooled to room temperature and quenched by the addition of aqueous $NaHCO_3$ (10 cm^3, 20% w/v). The resulting brown mixture was stirred for 3 hours over ether (10 cm^3) and extracted into ether (3 x 20 cm^3). The combined ethereal extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. TLC of the resultant oil showed two spots. The major spot was isolated and shown by ^1H NMR to be starting material (**200**) (65 mg). The more polar spot was isolated in 5 mg but could not be characterised.

3.11 Attempted Synthesis of Glycal nitrile oxide precursors.

3.11.1 Synthesis of 3,4,5-tri-*O*-acetyl-2,6-anhydro-β-D-xylopyranosylnitrile (221)

Sample code: KWB137
Molecular formula: $C_{12}H_{15}NO_7$
Molecular weight 285



221

Using the procedure of Koll *et al,*[174] 3,4,5-tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**128**) (150 mg, 0.47 mmole, 1 equiv.), was dissolved in pyridine (3 cm^3) and cooled to 0°C (ice-bath). To this PCl_3 (0.045 cm^3, 0.52 mmole, 1.1 equiv.) was added drop-wise and the mixture allowed to stir overnight. The resultant brown solution was re-cooled and ice cold 1M HCl added (20 cm^3) carefully and the mixture stirred for a further 20 minutes. The solution was extracted with chloroform (3 x 10 cm^3), the organic layers combined and washed with $NaHCO_3$ (2 x 10 cm^3), water (10 cm^3) and dried ($MgSO_4$). Removal of solvent *in vacuo* gave

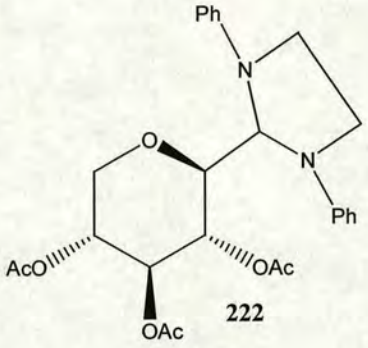
the product, 2,6-anhydro-3,4,5-tri-*O*-acetyl-D-xylopyranosylnitrile (**221**), as a white solid (114 mg, 85%); mp 128–129 °C (lit.[176] 131-132 °C); $[\alpha]^{18}_{D}$ –36.7 (c = 1.0 $CHCl_3$) {lit.[176] $[\alpha]^{18}_{D}$ –57.9 (c 0.8, $CHCl_3$)}; δ_H (250 MHz, $CDCl_3$) 2.03, 2.06, 2.07 (9H, 3 x s, 3 x $COCH_3$), 3.56 (1H, dd, 6b-H), 4.18 (1H, dd, 6a-H), 4.46 (1H, d, 2-H), 4.86 (1H, m, 5-H), 5.04 – 5.07 (2H, m, 3-H, 4-H); *J*(x,y)/Hz 2-3 6.9, 3-4 nd, 4-5 nd, 5-6a 4.01, 5-6b 6.8, 6a-6b 12.4; δ_C (63 MHz, $CDCl_3$) 20.3, 20.5 ($COCH_3$), 65.1 (C-6), 65.3, 66.8, 67.6, 68.7 (C-2, C-3. C-4. C-5), 114.3 (C≡N), 168.8, 169.2, 169.4 (C=O)

3.11.2 Synthesis of 1,3-diphenyl-2-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)imidazolidine (222)

Sample code: KWB180

Molecular formula: $C_{26}H_{30}N_2O_7$

Molecular weight: 482



222

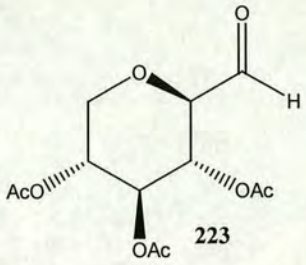
Using the procedure of Lehmann *et al*[166], Raney nickel (2 g) was added to a vigorously stirred solution of pyridine (10 cm^3), acetic acid (6 cm^3) and water (6 cm^3). Sodium hypophosphite monohydrate (1 g, 9.94 mmole) and *N,N'*-diphenylethylenediamine (0.68 g, 5.06 mmole) were added along with 3,4,5-tri-*O*-D-xylopyranosylnitrile (**221**) (300 mg, 1.05 mmole). The reaction mixture was allowed to stir for 16 hrs, insoluble material was then removed by filtration and washed with dichloromethane (40 cm^3). The organic layer was isolated, washed with water (6 x 10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil. The product, 1,3-diphenyl-2-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)imidazolidine (**222**), was isolated by dry flash chromatography eluting from hexane/ether (380 mg, 79%); mp 97-99 °C; $[\alpha]^{18}_{D}$ 10.9 (c = 0.76 $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.96, 1.99, 2.03 (9H, 3 x s, 3 x $COCH_3$), 3.20 (1H, t, 6a-H), 3.47 – 3.68 (4H, m, NCH_2CH_2N), 3.83 (1H, dd, 2-H), 4.21 (1H, dd, 6b-H), 4.91 (1H, m, 5-H), 4.98 – 5.11 (2H, m, 3-H, 4-H), 5.42 (1H, s, 1-H), 6.67 – 7.32 (10H, m, ArH); *J*(x,y)/Hz 2-3 9.6, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b 5.6, 6a-6b 11.0; δ_C (63 MHz, $CDCl_3$) 20.6, 20.7 (3 x $COCH_3$), 46.4, 47.1 (NCH_2CH_2N), 66.5 (C-6), 68.7, 69.8, 74.6, 75.5 (C-2, C-3, C-4, C-5) 79.0 (C-1), 112.7, 113.7, 117.8, 118.2, 129.2. 129.3 (ArH), 145.5, 146.4 (ArC), 168.7, 168.7, 170.5 (3 x $COCH_3$); *m/z* (FAB) Found: M^++H, 483.21335 $C_{26}H_{31}N_2O_7$ requires M^++H 483.21313.

3.11.3 Synthesis of 3,4,5-tri-*O*-acetyl-2,6-anhydro-*D-gulo*-heptose (223)

Sample code: KWB182

Molecular formula: $C_{12}H_{16}O_8$

Molecular weight: 288



223

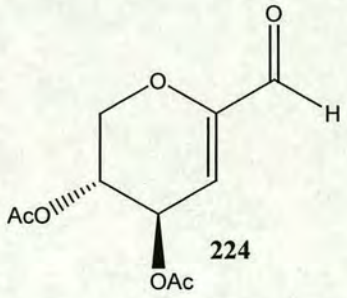
To a solution of 1,3-diphenyl-2-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)imidazolidine (170 mg, 0.35 mmole) in dichloromethane (4 cm^3) was added a solution of *p*-toluenesulfonic acid monohydrate (183 mg, 0.96 mmole, 2.75 equiv.) in acetone (1 cm^3). After stirring for 20 minutes, the precipitate was removed by filtration and washed with dichloromethane (50 cm^3). The filtrate was washed with water (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to give 3,4,5-tri-*O*-acetyl-2,6-anhydro-*D-gulo*-heptose, as an oil (66.7 mg, 60%); ν_{max}/cm^{-1} (DCM) 1739 (C=O ester and aldehyde); δ_H (250 MHz, $CDCl_3$) 2.00, 2.01, 2.13 (9H, 3 x s, 3 x $COCH_3$), 3.38 (1H, dd, 6a-H), 3.77 (1H, dd, 2-H), 4.20 (1H, dd, 6b-H), 4.94 (1H, m, 5-H), 5.03 – 5.26 (2H, m, 3-H, 4-H), 9.50 (1H, d, 1-H); *J*(x,y)/Hz 1-2 1.5, 2-3 9.3, 3-4 nd, 4-5 nd, 5-6a nd, 5-6b 5.6, 6a-6b 11.4; δ_C (63 MHz, $CDCl_3$) 20.4, 20.5 (3 x $COCH_3$), 66.0 (C-6), 67.4, 68.2, 72.0 (C-3, C-4, C-5), 80.3 (C-2), 169.5, 169.6, 169.8 (3 x $COCH_3$), 196.0 (C-1); *m/z* (FAB) Found: M^++H, 289.09345 $C_{12}H_{17}NO_8$ requires M^++H 289.09234.

3.11.4 Synthesis of 4,5-tri-*O*-acetyl-2,6-anhydro-3-deoxy-*aldehydo-D-threo*-hept-2-enose (224)

Sample code: KWB183

Molecular formula: $C_{10}H_{12}O_6$

Molecular weight: 204



224

3,4,5-tri-*O*-acetyl-β-D-xylopyranosyl aldehyde (**223**) (67 mg, 0.23 mmole) was dissolved in pyridine (5 cm^3) and acetic acid (5 cm^3) and left to stir at room temperature for 5 days. Removal of solvent *in vacuo* with co-evaporation with tolouene gave 4,5-tri-*O*-acetyl-2,6-anhydro-3-deoxy-*aldehydo-D-threo*-hept-2-enose (**224**) as a colourless oil (40 mg, 76%);

ν_{max}/cm^{-1} (DCM) 1745 (C=O ester), 1709 (C=O, α,β-unsaturated aldehyde), 1643 (C=C in conjunction with aldehyde group); δ_H (250 MHz, $CDCl_3$) 2.06, 20.9 (6H, 2 x s, 2 x $COCH_3$), 4.04 (1H, dd, 6a-H), 4.40 (1H, m, 6b-H), 5.02 (1H, ddd, 5-H), 5.19 (1H, m 4-H), 5.94 (1H, dd, 3-H), 9.24 (1H, s, 1-H); *J*(x,y)/Hz 3-4 5.0, 4-5 nd, 5-6a nd, 5-6b 4.8, 6a-6b 12.4; δ_C (63 MHz, $CDCl_3$) 20.7, 20.7 (2 x $COCH_3$), 63.2, 66.3 (C-4, C-5), 64.3 (C-6), 113.0 (C-3), 153.2 (C-2), 169.4, 169.5 (2 x $COCH_3$), 186.4 (C-1).

3.12 Protection reactions

Various strategies for hydroxyl protection were utilised.

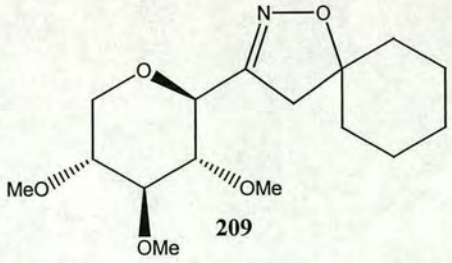
3.12.1 Introduction of methyl ether protection

Using the general procedure set out below, methyl ether protection was achieved to give compounds (**209**) and (**206**).

General procedure: Powdered KOH (4 equiv. per OH) was added to DMSO (2 cm^3) and stirred for 10 minutes. To this mixture was added the isoxazoline (1 equiv.) and the mixture stirred for a further 10 minutes. Finally MeI (2 equiv. per OH) was added and the mixture stirred for 20 minutes. The reaction was the poured into water, extracted with DCM (3 x 50 cm^3), the organic layers combined, washed with water (3 x 50cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was isolated by dry flash chromatography.

3.12.1.1 Formation of 5-(spirocyclohexyl)-3-(2,3,4-tri-*O*-methyl--β-D-xylopyranosyl)-2-isoxazoline (209)

Sample code: KWB169
Molecular formula: $C_{16}H_{27}NO_5$
Molecular weight: 313

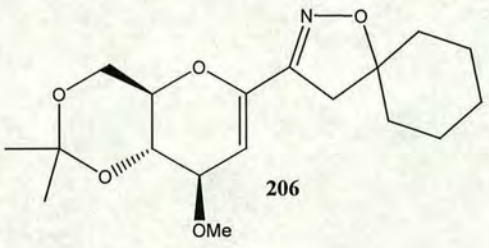


209

The isoxazoline (**210**) (50 mg, 0.18 mmole, 1 equiv.) was added to the suspension of powdered KOH (124 mg, 2,2 mmole, 12 equiv.) in DMSO (2 cm^3) followed by methyl iodide (0.07 cm^3, 1.08 mmole, 6 equiv.). Removal of solvent *in vacuo* yielded the product (**209**) (42 mg, 75%); mp 98-99 °C; δ_H (250 MHz, $CDCl_3$) 1.22-1.73 (10H, m, 6-H to 10-H), 2.67 (2H, dd, 4a-H, 4b-H) 3.06 – 3.25 (4H, m, 5a'-H, 5b'-H, 1'-H, 4'-H), 3.46, 3.48, 3.64 (9H, 3 x S, 3 x OC*H*$_3$), 3.90 (1H, dd, $J_{1,2}$ 9.4, 2'-H), 4.01 (1H, dd, $J_{2,3}$ 10.7, $J_{3,4}$ 5.7 3'-H); δ_C (63 MHz, $CDCl_3$): 23.2, 24.8, 36.1, 36.3(C-6 to C-10), 43.9 (C-4) 58.7, 60.1, 60.7 (3 x O*C*H$_3$), 67.5 (C-5'), 75.2, 79.5, 80.7, 87.2 (C-1' to C-4') 86.4 (C-5) 155.6 (C-4); *m/z* (FAB) Found: M^+ +1, 314.19674, $C_{16}H_{28}NO_5$ requires 314.19675.

3.12.1.2 Formation of 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-3-*O*-methyl-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (206)

Sample code: KWB 187
Molecular formula: $C_{18}H_{27}NO_5$
Molecular weight: 337



206

The glycal (**200**) (130 mg, 0.4 mmole) was added to a suspension of KOH (90 mg, 1.6 mmole, 4 equiv.) in DMSO (6 cm^3) followed by methyl iodide (0.04 cm^3, 0.8 mmole, 2 equiv.). Removal of solvent gave an oil which was purified by dry flash chromatography to give the product (**206**) as a white solid (47 mg, 42%); mp 120-122 °C; (250 MHz, $CDCl_3$) 1.26 to 1.79 (10H, m, 6-H to 10-H), 1.47, 1.57 (6H, 2 x s, $C(CH_3)_2$) 2.80 (2H, d, 4a-H, 4b-H), 3.50 (3H, s, OMe), 3.85 (1H, m, 6a'-H), 3.94 to 4.03 (2H, m, 6b'-H, 4'-H), 4.10 (2H, m, 3'-H, 5'H) 5.15 (1H, d, J_{2-3} 2.3 2'-H); δ_C (63 MHz, $CDCl_3$) 18.9, 28.8 (2 x $C(CH_3)_2$), 23.2, 23.2, 24.8, 36.1, 36.1 (C-6 to C-10), 43.7 (C-4), 57.4 (OMe), 61.4 (C-6') 69.8, 71.3, 75.7 (C-2', C-3', C-4') 87.9 (C-5), 99.5($C(CH_3)_2$), 104.7 (C-2'), 146.1 (C-1'), 151.6 (C-3); *m/z* (FAB) Found: M^+ +1, 338.19644, $C_{18}H_{28}NO_5$ requires 338.19675.

3.12.2 Introduction of acetate protection

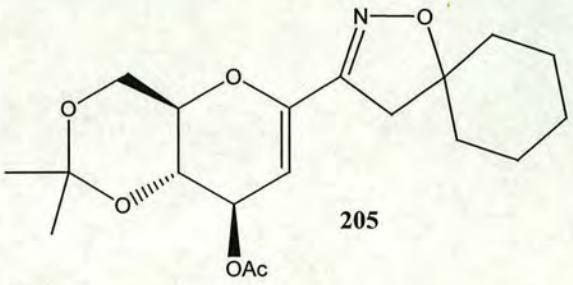
Compound (**200**) was acetylated as described below:

3.12.2.1 Acetate protection of 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (200)

Sample code: KWB117

Molecular formula: $C_{19}H_{27}NO_6$

Molecular weight: 365



205

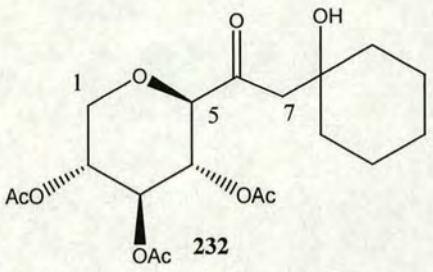
To the glycal (**200**) (100 mg, 0.3 mmole) in DCM (2 cm^3) was added triethylamine (0.33 cm^3, 2.3 mmole, 7.5 equiv.). DMAP (1.4 mg, 0.0012 mmole, 0.04 equiv.) was added and the solution cooled (ice-bath). After a 10 minutes stir, acetic anhydride (0.22 cm^3, 2.3 mmole, 7.5 equiv.) was added and the reaction mixture allowed to stir overnight protected from moisture (N_2). The mixture was poured into water, stirred for 1 hour, extracted with DCM (3 x 50 cm^3), the organic layers combined, washed with $NaHCO_3$ (3 x 50 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. Baseline impurities were removed by passing the oil obtained in ether through a pad of silica. Thus, 5-(spirocyclohexyl)-3-(4,6-*O*-isopropylidene-3-*O*-acetyl-2-deoxy-1,2-didehydro-D-*arabino*-hexo-pyranosyl)-2-isoxazoline (**205**) was obtained as white solid (93 mg, 82%); mp 82-84 °C; δ_H (250 MHz, $CDCl_3$) 1.28-1.78 (10H, m, 6a-H to 10b-H), 1.46, 1.46 (6H, 2 x s, 2 x CH_3), 2.78 (2H, s, 4a-H, 4b-H), 3.91 – 4.02 (2H, m, 6a'-H, 6b'-H), 4.08 - 4.15 (2H, m, 4'-H, 5'-H), 5.12 (1H, d, 2-H'), 5.45 (1H, dd, 3'-H); *J*(x,y)/Hz 2'-3' 2.5, 3'-4' 7.9, 4'-5' 4.9, 5'-6a' nd, 5'-6b' 9.9, 6a'-6b' 10.4; δ_C (63 MHz, $CDCl_3$) 18.8, 28.7 (2 x CCH_3), 21.1 ($COCH_3$), 23.1, 23.2, 24.7, 28.7, 36.1 (C-6 to C-10), 43.6 (C-4),61.3 (C-6') 68.9, 69.7, 70.0 (C-2', C-3', C-4') 88.2 (C-5), 99.7 (CCH_3), 103.5 (C-2'), 147.0 (C-1'), 151.4 (C-3), 170.8 ($COCH_3$); *m/z* (FAB) Found: M^+ +1 366.19164 $C_{12}H_{27}NO_6$ requires 366.19166.

3.13 Reductive hydrolytic cleavage of 2-isoxazolines to β-hydroxyketones

Two β-hydroxyketones were prepared from isoxazolines (**160**) and (**155**) by palladium charcoal and Raney nickel hydrogenolysis respectively.

3.13.1 Palladium charcoal hydrogenolysis of 5-(spirocylcohexy)-3-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-2-isoxazoline (160)

Sample code: KWB287
Molecular formula $C_{19}H_{28}O_9$
Molecular weight: 400

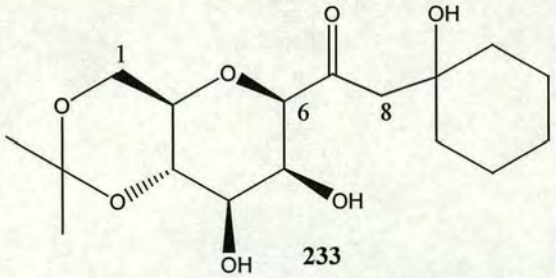


232

The isoxazoline (**160**) (250 mg, 0.63 mmole, 1 equiv.) was suspended in water (6 cm^3) and methanol (12 cm^3) and THF (15 cm^3) added until the isoxazoline dissolved. Then boric acid (235 mg, 3.79 mmole, 6 equiv.) and Pd/C (5%, 100mg) were added and the mixture degassed 3 times and left under an atmosphere of hydrogen for 24 hours. The catalyst was then removed by filtration through a celite pad, and the solvent removed *in vacuo* to give an oil which was purified by dry flash chromatography to give a white solid (**232**) (34 mg, 14%) and recovered starting material (**160**) (47 mg) along with an unidentified baseline material (30 mg) that gave a positive result with ninhydrin; δ_H (360 MHz, $CDCl_3$) 1.17 –1.69 (10H, m, 6-H to 10-H), 2.00, 2.02, 2.03(9H, 3 x s, 3 x $COCH_3$), 2.76 (2H, d, 7a-H, 7b-H), 3.09 (1H, br s, OH) 3.32 (1H, q, 1ax-H), 3.71 (1H, d, 5-H), 4.20 (1-H, dd, 1eq-H), 4.97 (1H, ddd, 2-H,), 5.07 (1H, dd, 4-H), 5.23 (1H, dd, 3-H); *J*(x,y)/Hz 1aq–1 eq 11.3, 1ax-2 10.2, 1eq-2 5.5, 2-3 9.4, 3-4 9.2, 4-5 9.7; δ_C (63 MHz, $CDCl_3$) 20.7, 20.8 (3 x $COCH_3$), 22.0, 25.7, 37.4, 37.9 (C-6 to C-10), 48.04 (C-4), 66.6 (C-5'), 68.6, 68.8, 72.8, 82.4 (C-1' to C-4'), 70.9 (C-5), 169.8, 170.0, 170.2 (3 x $COCH_3$) 207.3 (C-3); *m/z* (FAB) Found: M^+ +1 401.14888 $C_{19}H_{29}O_9$ requires 401.16193. M-18 peak at 383 amu.

3.13.2 Raney nickel hydrogenolysis of 5-(spirocylcohexy)-3-(2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosyl)-2-isoxazoline (155)

Sample code: KWB181
Molecular formula: $C_{17}H_{28}O_7$
Molecular weight: 344



233

The isoxazoline (**155**) (150 mg, 0.39 mmole) was dissolved in methanol (25 cm^3) and water (8 cm^3). To this boric acid (146 mg, 2.34 mmole, 6 equiv.) along with 6 spatula tips of Raney nickel (prepared by washing with methanol 20 times and storing at 0°C for 3 weeks) was added and the reaction mixture degassed 3 times and placed under an atmosphere of hydrogen. After an 24 hours stir the catalyst was removed by filtration through a celite pad. The solvent was then removed *in vacuo* and the resulting oil purified by dry flash column chromatography to give the partially deprotected product (**233**) as an oil (83 mg, 62%) along with an unidentified by-product (47 mg); δ_H (250 MHz, $CDCl_3$) 1.15 – 1.82 (10H, m, 10-H to 15-H), 1.40, 1.50 (6H, 2 x s, $(CH_3)_2$), 2.69 (2H, d, 8a-H, 8b-H), 2.72 (1H, br s, OH), 3.23 (1H, dt, 1b-H), 3.40 (1H, d, 6-H), 3.46 (1H, m 1a-H), 3.77 (2H, m, 5-H, 4-H), 3.91 (2H, m, 2-H, 3-H); δ_C (63 MHz, $CDCl_3$) 19.04, 28.9 (CCH_3) 21.74, 25.5, 34.5, 37.5 (C-6 to C-10), 47.6 (C-4), 61.9 (C-6'), 69.3, 71.3, 75.6, 81.0 (C-1' to C-5'), 70.6 (C-5), 99.9 (CCH_3), 209.9 (C-3).

3.14 Addition reactions on nitrile oxides

Addition of 4-tolylmethanethiol, thiophenol and aniline to 2,3,4,6-tetra-*O*-acetyl-β-glucopyranosylnitrile oxide (**115**) was carried out using the general procedure described below.

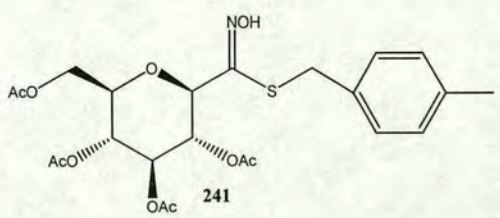
General Procedure: The hydroximoyl chloride (1 equiv.) was dissolved in dry ether (5 cm^3). To this the nucleophile (1 – 3 equiv.) was added and the mixture stirred protected from moisture (N_2). Then triethylamine (3 equiv.) was added *via* syringe pump over a 24 hr period and the reaction left for a further 6 hrs. It was then poured into water (50 cm^3), extracted with DCM (3 x 50cm^3), the organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was isolated from by-products using dry flash chromatography.

3.14.1 Addition Reaction of 4-tolylmethane thiol with 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol (139).

Sample code: KWB301

Molecular formula: $C_{23}H_{29}NO_{10}S$

Molecular weight: 511

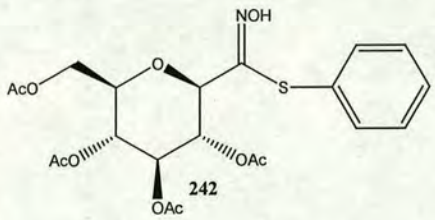


241

To the hydroximoyl chloride (**139**) (100 mg, 0.247 mole) in dry ether (5 cm^3) was added 4-tolylmethane thiol (0.034 cm^3, 0.247 mmole, 1 equiv.) followed by triethylamine (0.1 cm^3, 0.741 mmole, 3 equiv.) in accordance with the general procedure above. The product (**241**) was isolated by dry flash chromatography as a white solid (95 mg, 79%); $[\alpha]_D^{18}$ –21.4 (*c* = 1.49, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.98, 2.03, 2.05, 2.09 (12H, 4 x s, 4 x COC*H*$_3$), 2.35 (3H, s, ArC*H*$_3$), 3.72 (1H, ddd, 6-H), 4.11 – 4.36 (5H, m, 7a-H, 7b-H, 2-H, *CH*$_2$Ar), 5.08 - 5.31 (2H, m, 4-H, 5-H), 5.51 (1H, t, 3-H), 7.13 – 7.30 (5H, m, ArH), 8.96 (1H, br s, OH); *J*(x,y)/Hz 2-3 9.9, 3-4 9.2, 4-5 9.8, 5-6 9.6, 6-7a 2.6, 6-7b 5.0, 7a-7b 12.4; δ_C (90 MHz, $CDCl_3$) 20.4, 20.5, 20.6 (4 x COC*H*$_3$), 21.0 (ArC*H*$_3$), 34.3 (*C*H$_2$Ar), 62.1 (C-7), 68.0, 69.1. 74.1, 75.7, 77.7 (C-2 to C-6), 128.7, 129.3 (ArH), 132.9, 137.4 (Ar*C*), 148.7 (C-1), 169.4, 169.4, 170.4, 170.6 (4 x *C*OCH$_3$); *m/z* (FAB) Found: M^++H, 512.15944 $C_{23}H_{30}NO_{10}S$ requires M^++H 512.15904.

3.14.2 Addition Reaction of thiophenol with 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol (139).

Sample code: KWB316
Molecular formula: $C_{21}H_{26}NO_{10}S$
Molecular weight: 483



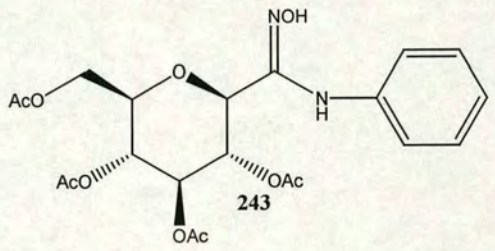
To the hydroximoyl chloride (**139**) (96 mg, 0.235 mole) in dry ether (5 cm^3) was added thiophenol (0.04 cm^3, 0.47 mmole, 2 equiv.) followed by triethylamine (0.1 cm^3, 0.75 mmole, 3 equiv.) in accordance to the general procedure above. The product (**242**) was isolated by dry flash chromatography as an white foam (96 mg, 85%); δ_H (250 MHz, $CDCl_3$) 1.90, 1.90, 1.92, 2.05 (12H, 4 x s, 4 x COC*H*$_3$), 2.79 (1H, ddd, 6-H), 3.67 (1H, d, 2-H), 3.85 (1H, dd, 7a-H), 4.01 (1H, dd, 7b-H) 4.83 – 4.99 (2H, m, 4-H, 5-H), 5.38 (1H, dd, 3-H), 7.20 – 7.62 (5H, m, ArH), 8.96 (1H, br s, OH); *J*(x,y)/Hz 2-3 9.8, 3-4 9.2, 4-5 10.0, 5-6 9.7, 6-7a 2.4, 6-7b 4.5, 7a-7b 12.2; δ_C (90 MHz, $CDCl_3$) 20.4, 20.5, 20.7 (4 x COC*H*$_3$), 61.7 (C-7), 67.6, 68.6, 74.3, 74.5, 75.4 (C-2 to C-6), 127.2(ArC), 129.1, 130.0, 136.5 (ArH), 148.6 (C-1), 169.1, 169.3, 170.5, 170.5 (4 x *C*OCH$_3$); *m/z* (FAB) Found: M^++H, 484.12738 $C_{23}H_{30}NO_{10}S$ requires M^++H 484.12774.

3.13.3 Addition Reaction of aniline with 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol (139)

Sample code: KWB324

Molecular formula: $C_{21}H_{26}N_2O_{10}$

Molecular weight: 466



243

Following a modified version of the general procedure, aniline (0.07 cm^3, 0.74 mmole, 3 equiv.) and triethylamine (0.07 cm^3, 0.494 mmole, 2 equiv.) were added *via* syringe pump over a 24 hour period to the hydroximoyl chloride (**139**) (100 mg, 0.247 mole) in dry ether (5 cm^3). The product (**243**) was isolated by dry flash chromatography as solid (30 mg, 26%) along with furoxan (40 mg); mp = 80-82 °C; $[\alpha]_D^{18}$ –27.4 (*c* = 1.06, $CHCl_3$); δ_H (250 MHz, $CDCl_3$), 2.16, 2.17. 2.18, 2.30 (12H, 4 x s, 4 x $COCH_3$), 3.72 (1H, ddd, 6-H), 4.22 – 4.36 (2H, m, 7a-H, 7b-H), 4.40 (1H, d, 2-H), 5.18 – 5.32 (2H, m, 4-H, 5-H), 5.66 (1H, dd, 3-H), 7.25 – 7.70 (5H, m, ArH), 8.47 (1H, br s, OH); *J*(x,y)/Hz 2-3 10.1, 3-4 9.1, 4-5 nd, 5-6 9.4, 6-7a 2.4, 6-7b 5.7, 7a-7b 12.4. δ_C (90 MHz, $CDCl_3$) 20.4, 20.5, 20.6 (4 x $COCH_3$), 62.4 (C-7), 75.9, 74.4, 72.8, 68.2, 68.0 (C-2 to C-6), 123.7, 125.0, 129.2 (ArH), 138.1 (ArC), 146.5 (C-1), 169.1, 169.2, 170.3, 170.5 (4 x $COCH_3$); *m/z* (FAB) Found: M^++H, 467.16605 $C_{21}H_{27}N_2O_{10}$ requires M^++H 467.16657.

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Appendix 1 : X-ray data for oxime (138)

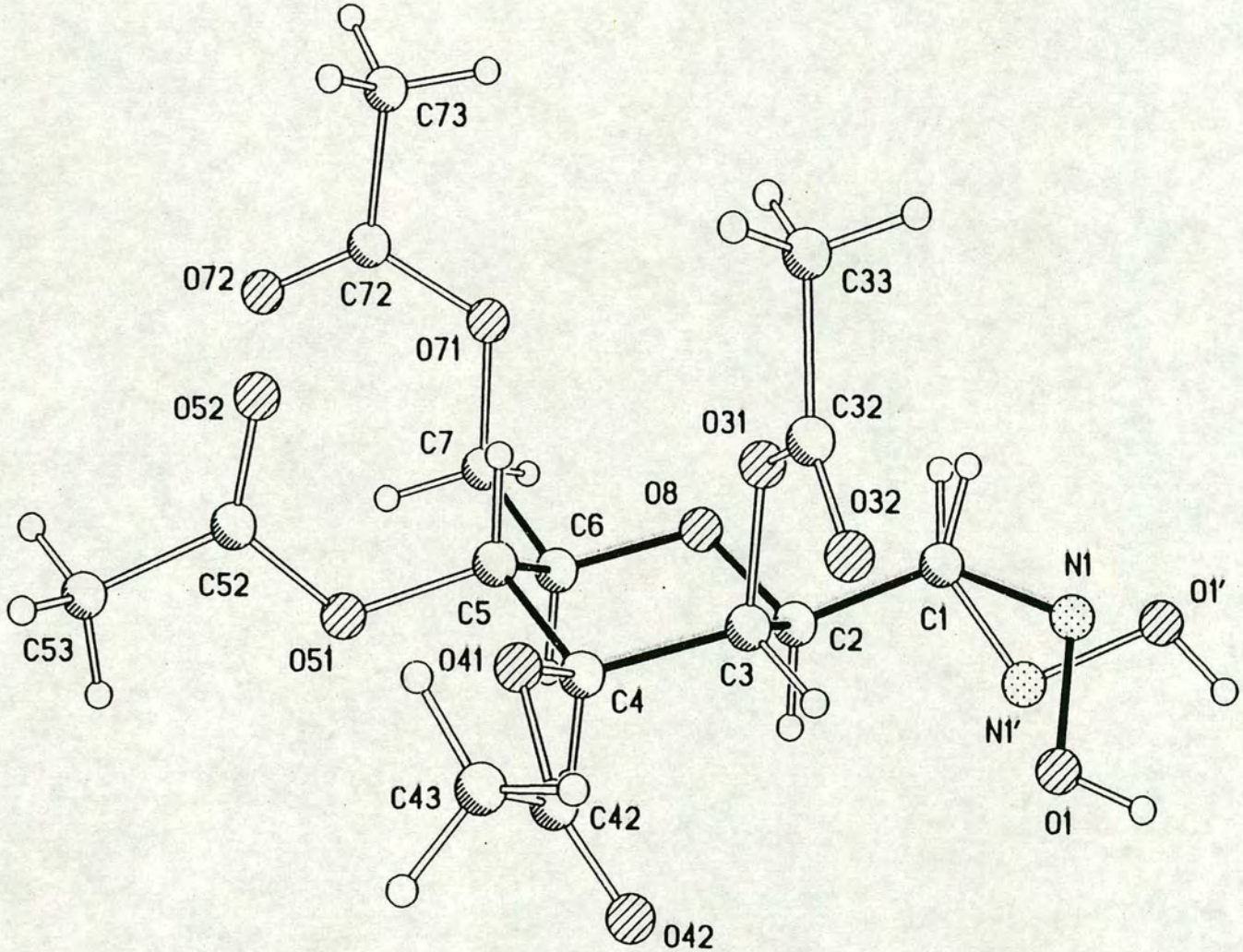

Table 1. Crystal data and structure refinement for KBXB09.

Contact	Simon Parsons, s.parsons@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C15 H21 N O10 Reaction No: KB09. Cis/trans disordered
Formula weight	375.33
Wavelength	1.54178 A
Temperature	220(2) K
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.179(2) A alpha = 90 deg. b = 10.831(2) A beta = 90 deg. c = 20.801(7) A gamma = 90 deg.
Volume	1842.8(9) A^3
Number of reflections for cell	54 (20 < theta < 22 deg.)
Z	4
Density (calculated)	1.353 Mg/m^3
Absorption coefficient	0.993 mm^-1
F(000)	792
B. DATA COLLECTION	
Crystal description	Colourless needle
Crystal size	0.78 x 0.19 x 0.12 mm
Theta range for data collection	4.25 to 70.13 deg.
Index ranges	-9<=h<=8, -12<=k<=13, -18<=l<=25
Reflections collected	2647
Independent reflections	1899 [R(int) = 0.0843]
Scan type	Omega-theta
Absorption correction	Psi-scans (Tmin= 0.719, Tmax=0.788)
C. SOLUTION AND REFINEMENT.	
Solution	direct (SHELXS-97 (Sheldrick, 1990))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	SHELXL-97
Hydrogen atom placement	geometric

Hydrogen atom treatment	riding
Data / restraints / parameters	1899/2/244
Goodness-of-fit on F^2	1.046
Conventional R [F>4sigma(F)]	R1 = 0.0611 [1496 data]
Weighted R (F^2 and all data)	wR2 = 0.1694
Absolute structure parameter	0.2(5)
Extinction coefficient	0.0031(8)
Final maximum delta/sigma	0.000

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.0970P)^2^+0.8393P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.308 and -0.217 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3) and site occupancies for nokb09. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)	Occ
C(1)	467(6)	348(5)	10521(2)	49(1)	1
N(1)	591(8)	-136(7)	11086(3)	53(2)	0.75
O(1)	2154(6)	190(6)	11326(2)	62(2)	0.75
N(1')	1180(20)	380(20)	11076(6)	60(6)	0.25
O(1')	30(20)	-258(16)	11463(9)	60(4)	0.25
C(2)	1618(6)	1036(5)	10105(2)	42(1)	1
C(3)	2956(6)	217(5)	9828(2)	38(1)	1
O(31)	2158(4)	-787(3)	9488(2)	39(1)	1
C(32)	2899(6)	-1913(5)	9505(2)	45(1)	1
O(32)	4104(5)	-2114(4)	9812(2)	66(1)	1
C(33)	2001(7)	-2800(5)	9093(3)	48(1)	1
C(4)	3980(6)	932(4)	9341(2)	37(1)	1
O(41)	5161(4)	161(3)	9027(2)	43(1)	1
C(42)	6538(6)	-76(5)	9379(3)	45(1)	1
O(42)	6752(4)	350(4)	9896(2)	58(1)	1
C(43)	7668(7)	-910(6)	9026(3)	65(2)	1
C(5)	2863(6)	1438(4)	8832(2)	38(1)	1
O(51)	3802(4)	2212(3)	8405(2)	48(1)	1
C(52)	4002(8)	1824(7)	7798(3)	64(2)	1
O(52)	3375(8)	888(5)	7590(2)	90(2)	1
C(53)	4959(12)	2728(8)	7421(4)	94(3)	1
C(6)	1569(6)	2260(5)	9144(2)	38(1)	1
C(7)	374(6)	2774(5)	8661(2)	45(1)	1
O(71)	-357(5)	1775(3)	8310(2)	52(1)	1
C(72)	-343(12)	1844(6)	7681(3)	78(2)	1
O(72)	123(13)	2714(5)	7385(2)	128(3)	1
C(73)	-984(16)	682(6)	7383(4)	122(4)	1
O(8)	651(4)	1555(3)	9597(2)	40(1)	1

Table 3. Bond lengths [A] and angles [deg] for nokb09.

C(1)-N(1)	1.290(8)
C(1)-N(1')	1.295(12)
C(1)-C(2)	1.481(7)
N(1)-O(1)	1.417(8)
N(1')-O(1')	1.419(12)
C(2)-O(8)	1.434(5)
C(2)-C(3)	1.522(7)
C(3)-O(31)	1.452(5)
C(3)-C(4)	1.526(7)
O(31)-C(32)	1.363(6)
C(32)-O(32)	1.194(6)
C(32)-C(33)	1.483(7)
C(4)-O(41)	1.434(6)
C(4)-C(5)	1.503(7)
O(41)-C(42)	1.368(6)
C(42)-O(42)	1.182(7)
C(42)-C(43)	1.486(8)
C(5)-O(51)	1.442(6)
C(5)-C(6)	1.528(6)
O(51)-C(52)	1.341(8)
C(52)-O(52)	1.215(9)
C(52)-C(53)	1.480(10)
C(6)-O(8)	1.426(6)
C(6)-C(7)	1.508(7)
C(7)-O(71)	1.437(6)
O(71)-C(72)	1.312(7)
C(72)-O(72)	1.188(9)
C(72)-C(73)	1.497(10)

N(1)-C(1)-N(1')	33.3(8)
N(1)-C(1)-C(2)	133.4(5)
N(1')-C(1)-C(2)	102.6(9)
C(1)-N(1)-O(1)	106.9(6)
C(1)-N(1')-O(1')	101.0(13)
O(8)-C(2)-C(1)	106.1(4)
O(8)-C(2)-C(3)	110.3(4)
C(1)-C(2)-C(3)	112.6(4)
O(31)-C(3)-C(2)	107.3(4)
O(31)-C(3)-C(4)	107.6(4)
C(2)-C(3)-C(4)	110.5(4)
C(32)-O(31)-C(3)	117.3(4)
O(32)-C(32)-O(31)	122.9(5)
O(32)-C(32)-C(33)	126.9(5)
O(31)-C(32)-C(33)	110.1(4)
O(41)-C(4)-C(5)	107.5(4)
O(41)-C(4)-C(3)	112.2(4)
C(5)-C(4)-C(3)	108.6(4)
C(42)-O(41)-C(4)	114.8(4)
O(42)-C(42)-O(41)	122.4(5)
O(42)-C(42)-C(43)	126.4(5)
O(41)-C(42)-C(43)	111.2(5)
O(51)-C(5)-C(4)	108.8(4)
O(51)-C(5)-C(6)	107.0(4)
C(4)-C(5)-C(6)	109.5(4)
C(52)-O(51)-C(5)	117.5(5)
O(52)-C(52)-O(51)	123.0(6)
O(52)-C(52)-C(53)	126.0(7)
O(51)-C(52)-C(53)	110.9(7)
O(8)-C(6)-C(7)	107.3(4)
O(8)-C(6)-C(5)	109.5(4)

C(7)-C(6)-C(5)	112.4(4)
O(71)-C(7)-C(6)	109.3(4)
C(72)-O(71)-C(7)	117.4(5)
O(72)-C(72)-O(71)	124.4(6)
O(72)-C(72)-C(73)	124.4(7)
O(71)-C(72)-C(73)	111.2(7)
C(6)-O(8)-C(2)	113.9(4)

Symmetry transformations used to generate equivalent atoms:

Appendix 2: X-ray data for furoxan (164)

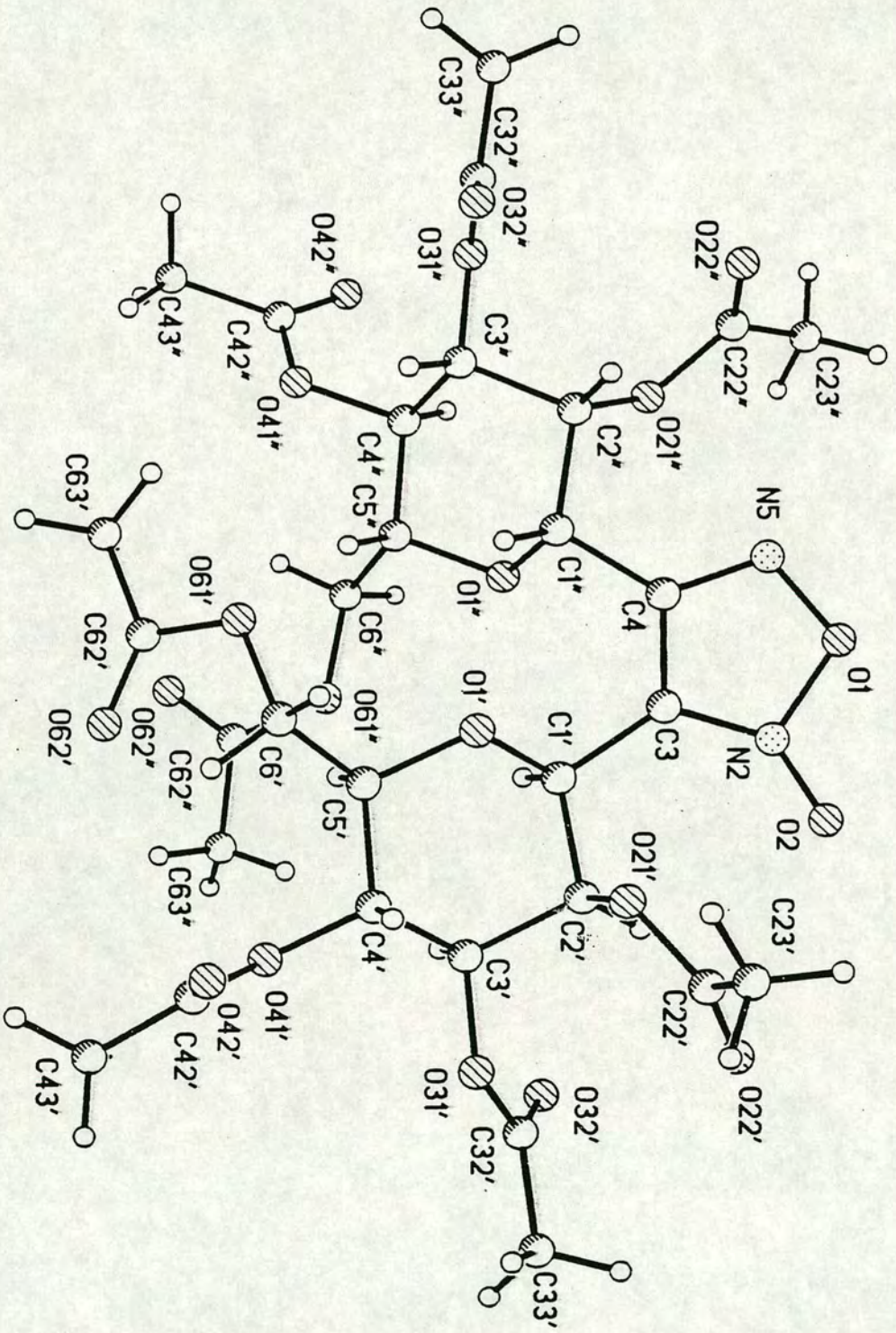

Table 1. Crystal data and structure refinement for kwb28x.

Contact	Simon Parsons, S.Parsons@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C30 H38 N2 O20 KWB28
Formula weight	746.62
Wavelength	1.54184 A
Temperature	150(2) K
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.839(3) A alpha = 97.803(11) deg. b = 8.6191(18) A beta = 97.599(16) deg. c = 13.229(3) A gamma = 91.07(2) deg.
Volume	877.2(4) A^3
Number of reflections for cell	50 (20 < theta < 22 deg.)
Z	1
Density (calculated)	1.413 Mg/m^3
Absorption coefficient	1.043 mm^-1
F(000)	392
B. DATA COLLECTION	
Crystal description	Colourless block
Crystal size	0.38 x 0.20 x 0.20 mm
Theta range for data collection	3.40 to 70.16 deg.
Index ranges	-9<=h<=9, -9<=k<=10, -15<=l<=16
Reflections collected	4052
Independent reflections	3093 [R(int) = 0.0293]
Scan type	Omega-theta
C. SOLUTION AND REFINEMENT.	
Solution	direct (SHELXS-97 (Sheldrick, 1990))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	SHELXL-97
Hydrogen atom placement	geometric
Hydrogen atom treatment	riding

Data / restraints / parameters	3093/3/470
Goodness-of-fit on F^2	1.038
Conventional R [F>4sigma(F)]	R1 = 0.0688 [2694 data]
Weighted R (F^2 and all data)	wR2 = 0.1904
Absolute structure parameter	0.2(4)
Extinction coefficient	0.0012(16)
Final maximum delta/sigma	0.000

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.1481P)^2^+0.2132P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.527 and -0.354 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for kwb28x. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	16065(7)	-4687(6)	2236(4)	56(1)
N(2)	14817(7)	-3923(6)	1558(4)	43(1)
O(2)	14763(8)	-4370(7)	670(4)	68(2)
C(3)	14100(7)	-2881(7)	2179(5)	39(1)
C(4)	14854(7)	-2964(7)	3205(5)	38(1)
N(5)	16003(7)	-4046(6)	3224(4)	45(1)
O(1')	11446(5)	-1833(5)	2471(3)	37(1)
C(1')	12800(8)	-1751(7)	1855(5)	37(1)
C(2')	12042(7)	-2031(7)	710(5)	36(1)
O(21')	11106(5)	-3539(5)	524(3)	40(1)
C(22')	11026(9)	-4352(9)	-425(5)	47(2)
O(22')	11645(7)	-3902(6)	-1115(4)	58(1)
C(23')	10043(13)	-5870(10)	-490(8)	69(2)
C(3')	10800(7)	-742(7)	541(5)	38(1)
O(31')	9963(5)	-932(5)	-509(3)	41(1)
C(32')	10912(9)	-427(8)	-1198(5)	47(2)
O(32')	12293(7)	215(7)	-953(4)	57(1)
C(33')	9969(10)	-800(12)	-2255(6)	61(2)
C(4')	9427(7)	-733(7)	1232(5)	38(1)
O(41')	8435(5)	623(5)	1097(3)	41(1)
C(42')	6692(7)	429(8)	965(5)	41(1)
O(42')	5948(5)	-757(6)	1025(4)	49(1)
C(43')	5867(11)	1924(11)	756(10)	78(3)
C(5')	10253(7)	-602(7)	2354(5)	37(1)
C(6')	8964(8)	-749(9)	3094(5)	45(2)
O(61')	9605(6)	-39(5)	4128(4)	44(1)
C(62')	9272(8)	1523(8)	4356(5)	46(2)
O(62')	8628(8)	2251(7)	3696(5)	64(2)
C(63')	9855(11)	2147(9)	5448(6)	60(2)
O(1")	14829(5)	-384(5)	3981(3)	36(1)
C(1")	14401(7)	-1964(7)	4126(5)	36(1)
C(2")	15236(7)	-2350(7)	5176(5)	35(1)
O(21")	17075(5)	-2226(5)	5201(3)	38(1)
C(22")	17958(8)	-3432(8)	5566(5)	44(2)
O(22")	17302(7)	-4408(7)	5953(5)	64(2)
C(23")	19803(8)	-3324(9)	5369(6)	55(2)
C(3")	14666(7)	-1146(7)	5993(5)	38(1)
O(31")	15517(5)	-1324(5)	6988(3)	40(1)
C(32")	14834(8)	-2462(8)	7440(5)	44(1)
O(32")	13601(7)	-3273(7)	7036(4)	58(1)
C(33")	15866(12)	-2601(12)	8468(7)	64(2)
C(4")	15036(7)	530(7)	5809(5)	37(1)
O(41")	14244(6)	1583(5)	6531(3)	46(1)
C(42")	15237(11)	2341(8)	7352(5)	50(2)
O(42")	16802(7)	2252(7)	7491(5)	67(2)
C(43")	14213(13)	3281(10)	8067(6)	64(2)
C(5")	14170(7)	725(7)	4733(5)	37(1)
C(6")	14477(9)	2345(8)	4451(5)	44(1)
O(61")	13376(6)	2463(5)	3491(3)	46(1)
C(62")	12514(7)	3799(7)	3436(5)	40(1)
O(62")	12563(6)	4823(6)	4154(4)	52(1)
C(63")	11465(10)	3810(10)	2404(6)	55(2)

Table 3. Bond lengths [A] and angles [deg] for kwb28x.

O(1)-N(5)	1.355(8)
O(1)-N(2)	1.465(7)
N(2)-O(2)	1.180(7)
N(2)-C(3)	1.319(8)
C(3)-C(4)	1.418(9)
C(3)-C(1')	1.486(8)
C(4)-N(5)	1.309(7)
C(4)-C(1")	1.482(8)
O(1')-C(1')	1.427(7)
O(1')-C(5')	1.438(7)
C(1')-C(2')	1.537(9)
C(2')-O(21')	1.456(7)
C(2')-C(3')	1.511(8)
O(21')-C(22')	1.346(8)
C(22')-O(22')	1.194(9)
C(22')-C(23')	1.492(12)
C(3')-O(31')	1.442(7)
C(3')-C(4')	1.500(8)
O(31')-C(32')	1.360(8)
C(32')-O(32')	1.191(8)
C(32')-C(33')	1.483(10)
C(4')-O(41')	1.435(7)
C(4')-C(5')	1.528(8)
O(41')-C(42')	1.359(7)
C(42')-O(42')	1.185(8)
C(42')-C(43')	1.495(11)
C(5')-C(6')	1.512(8)
C(6')-O(61')	1.441(8)
O(61')-C(62')	1.377(8)
C(62')-O(62')	1.206(9)
C(62')-C(63')	1.480(11)
O(1")-C(5")	1.437(6)
O(1")-C(1")	1.440(7)
C(1")-C(2")	1.536(8)
C(2")-O(21")	1.439(6)
C(2")-C(3")	1.512(8)
O(21")-C(22")	1.367(7)
C(22")-O(22")	1.185(9)
C(22")-C(23")	1.507(9)
C(3")-O(31")	1.424(7)
C(3")-C(4")	1.526(9)
O(31")-C(32")	1.353(8)
C(32")-O(32")	1.202(9)
C(32")-C(33")	1.508(11)
C(4")-O(41")	1.437(7)
C(4")-C(5")	1.526(8)
O(41")-C(42")	1.333(9)
C(42")-O(42")	1.222(10)
C(42")-C(43")	1.487(10)
C(5")-C(6")	1.517(9)
C(6")-O(61")	1.455(8)
O(61")-C(62")	1.352(7)
C(62")-O(62")	1.202(8)
C(62")-C(63")	1.499(9)

N(5)-O(1)-N(2)	108.7(4)
O(2)-N(2)-C(3)	139.7(6)
O(2)-N(2)-O(1)	115.2(5)
C(3)-N(2)-O(1)	105.1(5)
N(2)-C(3)-C(4)	108.3(5)

N(2)-C(3)-C(1')	125.8(6)
C(4)-C(3)-C(1')	125.8(5)
N(5)-C(4)-C(3)	110.6(5)
N(5)-C(4)-C(1")	124.8(6)
C(3)-C(4)-C(1")	124.6(5)
C(4)-N(5)-O(1)	107.3(5)
C(1')-O(1')-C(5')	112.1(4)
O(1')-C(1')-C(3)	107.0(5)
O(1')-C(1')-C(2')	109.4(5)
C(3)-C(1')-C(2')	115.2(5)
O(21')-C(2')-C(3')	109.6(5)
O(21')-C(2')-C(1')	107.2(5)
C(3')-C(2')-C(1')	106.7(5)
C(22')-O(21')-C(2')	116.9(5)
O(22')-C(22')-O(21')	124.2(7)
O(22')-C(22')-C(23')	125.3(7)
O(21')-C(22')-C(23')	110.4(6)
O(31')-C(3')-C(4')	107.9(5)
O(31')-C(3')-C(2')	111.1(5)
C(4')-C(3')-C(2')	111.3(5)
C(32')-O(31')-C(3')	115.1(5)
O(32')-C(32')-O(31')	123.0(6)
O(32')-C(32')-C(33')	127.1(7)
O(31')-C(32')-C(33')	109.9(6)
O(41')-C(4')-C(3')	107.0(5)
O(41')-C(4')-C(5')	109.0(5)
C(3')-C(4')-C(5')	109.9(5)
C(42')-O(41')-C(4')	117.5(5)
O(42')-C(42')-O(41')	124.2(6)
O(42')-C(42')-C(43')	125.5(6)
O(41')-C(42')-C(43')	110.4(6)
O(1')-C(5')-C(6')	107.0(5)
O(1')-C(5')-C(4')	109.7(5)
C(6')-C(5')-C(4')	113.3(5)
O(61')-C(6')-C(5')	112.3(5)
C(62')-O(61')-C(6')	115.3(5)
O(62')-C(62')-O(61')	120.9(7)
O(62')-C(62')-C(63')	126.6(7)
O(61')-C(62')-C(63')	112.5(6)
C(5")-O(1")-C(1")	110.6(4)
O(1")-C(1")-C(4)	105.2(4)
O(1")-C(1")-C(2")	111.9(5)
C(4)-C(1")-C(2")	116.4(5)
O(21")-C(2")-C(3")	110.1(5)
O(21")-C(2")-C(1")	107.8(4)
C(3")-C(2")-C(1")	107.3(4)
C(22")-O(21")-C(2")	115.1(5)
O(22")-C(22")-O(21")	122.9(5)
O(22")-C(22")-C(23")	127.4(6)
O(21")-C(22")-C(23")	109.7(6)
O(31")-C(3")-C(2")	111.0(5)
O(31")-C(3")-C(4")	107.6(5)
C(2")-C(3")-C(4")	112.4(5)
C(32")-O(31")-C(3")	115.2(5)
O(32")-C(32")-O(31")	122.9(6)
O(32")-C(32")-C(33")	126.0(7)
O(31")-C(32")-C(33")	111.1(6)
O(41")-C(4")-C(3")	108.5(5)
O(41")-C(4")-C(5")	107.2(4)
C(3")-C(4")-C(5")	108.2(5)
C(42")-O(41")-C(4")	118.5(5)
O(42")-C(42")-O(41")	123.1(7)
O(42")-C(42")-C(43")	124.8(7)
O(41")-C(42")-C(43")	112.1(7)

O(1")-C(5")-C(6")	107.4(5)
O(1")-C(5")-C(4")	109.6(4)
C(6")-C(5")-C(4")	113.1(5)
O(61")-C(6")-C(5")	107.8(5)
C(62")-O(61")-C(6")	116.9(5)
O(62")-C(62")-O(61")	122.7(6)
O(62")-C(62")-C(63")	125.0(6)
O(61")-C(62")-C(63")	112.2(6)

Symmetry transformations used to generate equivalent atoms:

Appendix 3: X-ray data for glycal (200)

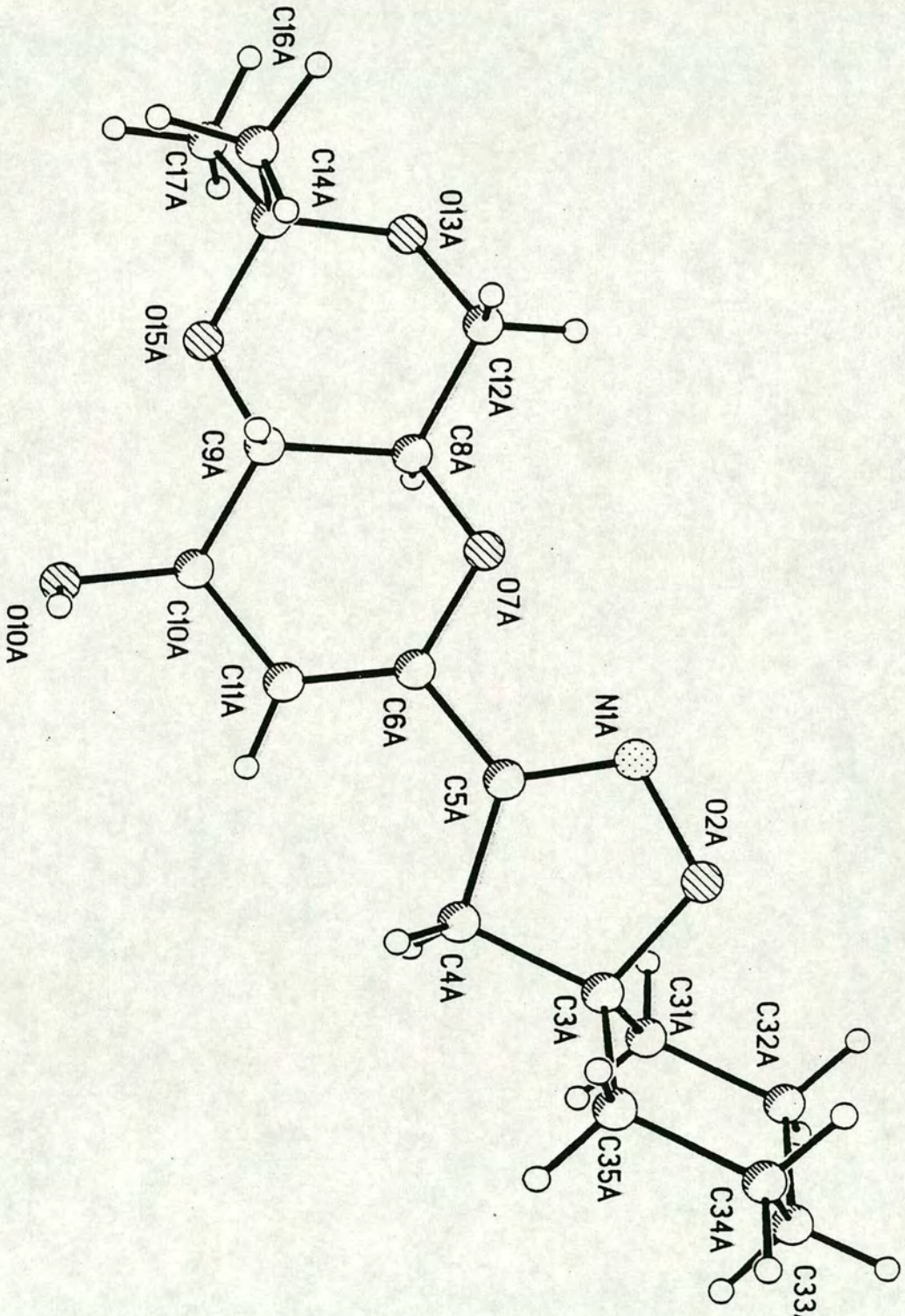

Table 1. Crystal data and structure refinement for kwb103.

Contact	Simon Parsons, S.Parsons@ed.ac.uk
A. CRYSTAL DATA	
Empirical formula	C17 H25 N O5 KWB103
Formula weight	323.38
Wavelength	0.71073 A
Temperature	150(2) K
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 11.968(3) A alpha = 90 deg. b = 9.876(2) A beta = 96.883(3) deg. c = 14.233(3) A gamma = 90 deg.
Volume	1670.2(6) A^3
Number of reflections for cell	6396 (2 < theta < 29 deg.)
Z	4
Density (calculated)	1.286 Mg/m^3
Absorption coefficient	0.094 mm^-1
F(000)	696
B. DATA COLLECTION	
Crystal description	Colourless tablet
Crystal size	0.34 x 0.34 x 0.14 mm
Instrument	CCD area detector
Theta range for data collection	2.68 to 28.99 deg.
Index ranges	-16<=h<=14, -13<=k<=13, -19<=l<=18
Reflections collected	12358
Independent reflections	7654 [R(int) = 0.0275]
Scan type	phi and omega scans
Absorption correction	Sadabs (Tmin= 0.720, Tmax=1)
C. SOLUTION AND REFINEMENT.	
Solution	direct (SHELXS-97 (Sheldrick, 1990))
Refinement type	Full-matrix least-squares on F^2

Program used for refinement	SHELXL-97
Hydrogen atom placement	geometric/difmap (OH,Me)
Hydrogen atom treatment	riding/rotating group (OH,Me)
Data / restraints / parameters	7654/1/421
Goodness-of-fit on F^2	0.896
Conventional R [F>4sigma(F)]	R1 = 0.0389 [6177 data]
Weighted R (F^2 and all data)	wR2 = 0.0800
Absolute structure parameter	0.5(6) - meaningless!
Final maximum delta/sigma	0.002

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.0376P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.253 and -0.183 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for kwb103. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1A)	9210(1)	7975(2)	9258(1)	29(1)
O(2A)	8914(1)	7920(1)	10181(1)	32(1)
C(3A)	9646(1)	8872(2)	10784(1)	26(1)
C(31A)	8969(2)	10153(2)	10890(1)	31(1)
C(32A)	7972(2)	9934(2)	11445(1)	40(1)
C(33A)	8372(2)	9310(2)	12403(1)	42(1)
C(34A)	8972(2)	7980(2)	12280(1)	36(1)
C(35A)	9971(2)	8174(2)	11723(1)	31(1)
C(4A)	10629(1)	9124(2)	10210(1)	31(1)
C(5A)	10131(1)	8632(2)	9254(1)	24(1)
C(6A)	10641(1)	8784(2)	8381(1)	24(1)
O(7A)	10013(1)	8157(1)	7629(1)	31(1)
C(8A)	10330(1)	8582(2)	6731(1)	28(1)
C(9A)	11595(1)	8472(2)	6738(1)	23(1)
O(10A)	13342(1)	9349(1)	7612(1)	30(1)
C(10A)	12162(1)	9501(2)	7424(1)	23(1)
C(11A)	11599(1)	9439(2)	8314(1)	25(1)
C(12A)	9727(1)	7701(2)	5963(1)	39(1)
O(13A)	10096(1)	8101(1)	5088(1)	36(1)
C(14A)	11274(1)	7973(2)	5068(1)	28(1)
O(15A)	11874(1)	8753(1)	5814(1)	24(1)
C(16A)	11648(2)	6495(2)	5105(1)	36(1)
C(17A)	11530(2)	8651(2)	4167(1)	38(1)
N(1B)	4083(1)	7508(1)	9251(1)	29(1)
O(2B)	3759(1)	7595(1)	10163(1)	36(1)
C(3B)	4559(2)	6807(2)	10826(1)	29(1)
C(31B)	3969(2)	5504(2)	11044(1)	32(1)
C(32B)	2940(2)	5774(2)	11557(1)	38(1)
C(33B)	3274(2)	6552(2)	12463(1)	46(1)
C(34B)	3843(2)	7882(2)	12263(1)	46(1)
C(35B)	4849(2)	7651(2)	11716(1)	41(1)
C(4B)	5556(2)	6562(2)	10269(1)	35(1)
C(5B)	5060(1)	6950(2)	9291(1)	27(1)
C(6B)	5626(1)	6868(2)	8442(1)	27(1)
O(7B)	4891(1)	6983(1)	7623(1)	31(1)
C(8B)	5425(1)	7496(2)	6845(1)	26(1)
C(9B)	6491(1)	6723(2)	6729(1)	24(1)
O(10B)	8224(1)	5949(1)	7608(1)	32(1)
C(10B)	7334(1)	6917(2)	7591(1)	26(1)
C(11B)	6738(1)	6814(2)	8462(1)	28(1)
C(12B)	4616(1)	7372(2)	5955(1)	31(1)
O(13B)	5156(1)	7866(1)	5183(1)	31(1)
C(14B)	6186(1)	7200(2)	5061(1)	28(1)
O(15B)	6944(1)	7241(1)	5923(1)	27(1)
C(16B)	5983(2)	5767(2)	4704(1)	35(1)
C(17B)	6736(2)	8062(2)	4375(1)	41(1)

Table 3. Bond lengths [A] and angles [deg] for kwb103.

N(1A)-C(5A)	1.280(2)
N(1A)-O(2A)	1.4017(15)
O(2A)-C(3A)	1.4860(19)
C(3A)-C(35A)	1.514(2)
C(3A)-C(31A)	1.519(2)
C(3A)-C(4A)	1.531(2)
C(31A)-C(32A)	1.523(2)
C(32A)-C(33A)	1.520(3)
C(33A)-C(34A)	1.517(3)
C(34A)-C(35A)	1.523(2)
C(4A)-C(5A)	1.499(2)
C(5A)-C(6A)	1.456(2)
C(6A)-C(11A)	1.329(2)
C(6A)-O(7A)	1.3797(19)
O(7A)-C(8A)	1.4379(18)
C(8A)-C(12A)	1.512(2)
C(8A)-C(9A)	1.516(2)
C(9A)-O(15A)	1.4221(18)
C(9A)-C(10A)	1.513(2)
O(10A)-C(10A)	1.4136(18)
C(10A)-C(11A)	1.506(2)
C(12A)-O(13A)	1.425(2)
O(13A)-C(14A)	1.4199(19)
C(14A)-O(15A)	1.4339(19)
C(14A)-C(17A)	1.510(2)
C(14A)-C(16A)	1.526(3)
N(1B)-C(5B)	1.287(2)
N(1B)-O(2B)	1.4021(16)
O(2B)-C(3B)	1.4819(19)
C(3B)-C(31B)	1.518(2)
C(3B)-C(35B)	1.522(2)
C(3B)-C(4B)	1.529(2)
C(31B)-C(32B)	1.527(2)
C(32B)-C(33B)	1.514(3)
C(33B)-C(34B)	1.522(3)
C(34B)-C(35B)	1.526(3)
C(4B)-C(5B)	1.496(2)
C(5B)-C(6B)	1.457(2)
C(6B)-C(11B)	1.330(2)
C(6B)-O(7B)	1.3780(18)
O(7B)-C(8B)	1.4349(18)
C(8B)-C(12B)	1.505(2)
C(8B)-C(9B)	1.513(2)
C(9B)-O(15B)	1.4213(18)
C(9B)-C(10B)	1.504(2)
O(10B)-C(10B)	1.4289(19)
C(10B)-C(11B)	1.505(2)
C(12B)-O(13B)	1.4262(19)
O(13B)-C(14B)	1.425(2)
C(14B)-O(15B)	1.4362(19)
C(14B)-C(17B)	1.505(2)
C(14B)-C(16B)	1.514(2)

C(5A)-N(1A)-O(2A)	109.80(13)
N(1A)-O(2A)-C(3A)	108.58(11)
O(2A)-C(3A)-C(35A)	107.04(13)
O(2A)-C(3A)-C(31A)	107.46(13)
C(35A)-C(3A)-C(31A)	112.02(14)
O(2A)-C(3A)-C(4A)	103.43(12)
C(35A)-C(3A)-C(4A)	114.36(15)

C(31A)-C(3A)-C(4A)	111.81(14)
C(3A)-C(31A)-C(32A)	113.20(14)
C(33A)-C(32A)-C(31A)	109.90(16)
C(34A)-C(33A)-C(32A)	110.48(14)
C(33A)-C(34A)-C(35A)	111.33(15)
C(3A)-C(35A)-C(34A)	112.44(15)
C(5A)-C(4A)-C(3A)	100.61(13)
N(1A)-C(5A)-C(6A)	120.37(15)
N(1A)-C(5A)-C(4A)	114.14(14)
C(6A)-C(5A)-C(4A)	125.38(15)
C(11A)-C(6A)-O(7A)	123.80(14)
C(11A)-C(6A)-C(5A)	124.41(15)
O(7A)-C(6A)-C(5A)	111.78(14)
C(6A)-O(7A)-C(8A)	112.43(12)
O(7A)-C(8A)-C(12A)	108.72(13)
O(7A)-C(8A)-C(9A)	110.05(13)
C(12A)-C(8A)-C(9A)	110.67(14)
O(15A)-C(9A)-C(10A)	109.16(12)
O(15A)-C(9A)-C(8A)	109.01(12)
C(10A)-C(9A)-C(8A)	109.06(13)
O(10A)-C(10A)-C(11A)	111.99(13)
O(10A)-C(10A)-C(9A)	114.30(13)
C(11A)-C(10A)-C(9A)	107.67(13)
C(6A)-C(11A)-C(10A)	123.90(15)
O(13A)-C(12A)-C(8A)	107.55(14)
C(14A)-O(13A)-C(12A)	113.93(13)
O(13A)-C(14A)-O(15A)	110.34(13)
O(13A)-C(14A)-C(17A)	106.30(14)
O(15A)-C(14A)-C(17A)	104.86(14)
O(13A)-C(14A)-C(16A)	111.87(15)
O(15A)-C(14A)-C(16A)	111.67(13)
C(17A)-C(14A)-C(16A)	111.46(15)
C(9A)-O(15A)-C(14A)	115.32(12)
C(5B)-N(1B)-O(2B)	109.66(13)
N(1B)-O(2B)-C(3B)	109.11(11)
O(2B)-C(3B)-C(31B)	107.11(14)
O(2B)-C(3B)-C(35B)	107.92(14)
C(31B)-C(3B)-C(35B)	111.02(14)
O(2B)-C(3B)-C(4B)	103.77(13)
C(31B)-C(3B)-C(4B)	112.55(15)
C(35B)-C(3B)-C(4B)	113.88(15)
C(3B)-C(31B)-C(32B)	111.82(14)
C(33B)-C(32B)-C(31B)	110.48(16)
C(32B)-C(33B)-C(34B)	110.88(16)
C(33B)-C(34B)-C(35B)	111.36(16)
C(3B)-C(35B)-C(34B)	113.04(16)
C(5B)-C(4B)-C(3B)	101.20(14)
N(1B)-C(5B)-C(6B)	119.80(15)
N(1B)-C(5B)-C(4B)	114.08(15)
C(6B)-C(5B)-C(4B)	125.82(15)
C(11B)-C(6B)-O(7B)	123.87(15)
C(11B)-C(6B)-C(5B)	123.28(15)
O(7B)-C(6B)-C(5B)	112.59(14)
C(6B)-O(7B)-C(8B)	112.52(12)
O(7B)-C(8B)-C(12B)	108.61(13)
O(7B)-C(8B)-C(9B)	111.42(13)
C(12B)-C(8B)-C(9B)	109.46(13)
O(15B)-C(9B)-C(10B)	109.26(13)
O(15B)-C(9B)-C(8B)	108.33(13)
C(10B)-C(9B)-C(8B)	109.80(13)
O(10B)-C(10B)-C(9B)	110.74(13)
O(10B)-C(10B)-C(11B)	111.51(13)
C(9B)-C(10B)-C(11B)	108.98(13)
C(6B)-C(11B)-C(10B)	123.48(15)

O(13B)-C(12B)-C(8B)	108.38(13)
C(14B)-O(13B)-C(12B)	114.46(12)
O(13B)-C(14B)-O(15B)	110.50(13)
O(13B)-C(14B)-C(17B)	105.65(14)
O(15B)-C(14B)-C(17B)	104.95(14)
O(13B)-C(14B)-C(16B)	111.51(14)
O(15B)-C(14B)-C(16B)	111.85(13)
C(17B)-C(14B)-C(16B)	112.02(15)
C(9B)-O(15B)-C(14B)	114.64(12)

Symmetry transformations used to generate equivalent atoms:

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TETRAHEDRON LETTERS

Generation and cycloaddition reactions of pyranose-1-carbonitrile oxides

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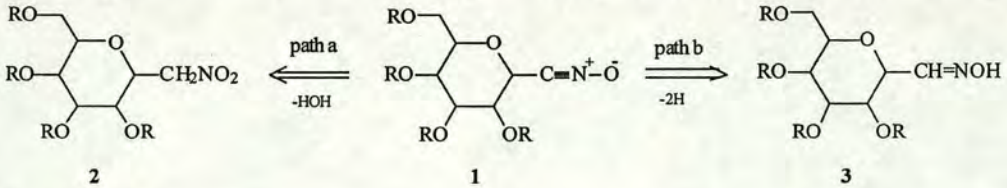
Abstract—Stannate(II) reduction of the β-D-glucopyranosylnitromethane derivative **4** affords aldoxime **5**, which provides access to the nitrile oxide **7**, either on treatment with aq. hypochlorite, or via conversion to the hydroximoyl chloride **11** followed by base-mediated dehydrohalogenation. D-Galactose-, D-mannose- and D-xylose-derived nitrile oxides are generated similarly. The nitrile oxides either dimerise to 3,4-dipyranosyl-1,2,5-oxadiazole *N*-oxides or are trapped as cycloadducts in the presence of dipolarophiles. © 2001 Elsevier Science Ltd. All rights reserved.

There is considerable current interest in the chemistry of *C*-glycosides,[1] and in methods for their synthesis in particular. One approach which has so far received little attention, but offers scope for the preparation of a variety of novel derivatives, makes use of nitrile oxide/isoxazoline chemistry,[2] and involves the generation of glycosyl nitrile oxides, their cycloaddition reactions with alkenes (or alkynes) and manipulation of the resulting isoxazoline (isoxazole) cycloadducts. In the literature there are occasional reports[3] of furanosyl nitrile oxide cycloadditions, and we have utilised[4,5] the pyranosyl analogues **1** as key intermediates in a synthetic sequence from readily accessible monosaccharide precursors to carbohydrate isoxazolines as precursors of carbon linked disaccharides (*C*-disaccharides). We previously employed[4,5] a modified Mukaiyama procedure[6] for generating pyranosyl nitrile oxides **1**, which involved tolylene diisocyanate-mediated dehydration of the corresponding nitromethyl compounds **2** (Scheme 1, path a). The Mukaiyama route, however, has several limitations. Firstly, the use of isocyanates as the dehydrating agent is incompatible with free hydroxyl groups in either reactant—a disadvantage in carbohydrate synthesis—and elevated temperatures (80–100°C) and/or prolonged reaction times (3–5 days) are often required to achieve high conversions, so the method is not ideal for low boiling and thermally unstable dipolarophiles. An alternative approach is therefore needed to overcome these deficiencies. We now report that carbohydrate nitrile oxides such as **1** can readily be generated form the corresponding oxime **3**, either by oxidation with aq. hypochlorite, or by base mediated dehydrohalogenation of its hydroximoyl chloride derivative (Scheme 1, path b).

The first requirement was to develop an effective route to the oximes.[7] The method selected was based on the observation[8] that primary aliphatic nitro compounds are reduced to aldoximes by stannate(II) complexes generated from $SnCl_2$/PhSH/Et_3N. Treatment of $SnCl_2$ (363 mg, 1.92 mmol) in dry THF (6 ml) at 0°C with Et_3N (648 mg, 6.40 mmol) and thiophenol (635 mg, 5.76 mmol) afforded a yellow solution of the stannate (II) complex $[Et_3NH][(PhS)_3Sn]$, to which was added a



Scheme 1.

Keywords: cycloadditions; *C*-glycosides; nitrile oxides; isoxazoles; isoxazolines.

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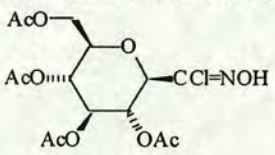
solution of β-D-glucopyranosyl-nitromethane derivative **4**[9] (500 mg, 1.28 mmol). After stirring for 16 h the solvent was removed in vacuo and the residue purified by chromatography (silica, hexane/Et_2O) and recrystallisation (hexane/Et_2O) to afford tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime (**5**)[10] as a 4:1 mixture of *E*- and *Z*-isomers[11] in a 76% combined yield. In the ^1H NMR spectrum there are characteristic doublet signals (*J* 6.8 Hz) for the imino proton of the *E*- and *Z*-isomers at 7.30 and 6.7 ppm, respectively, and corresponding broad singlet peaks at 8.40 and 8.62 ppm for the OH groups. D-Galactose-, D-mannose- and D-xylose-derived oximes were prepared similarly in 80–90% yields from the corresponding pyranosylnitromethanes.

The first method utilised for nitrile oxide generation involved oxidation of the oximes with aqueous hypochlorite.[12] In a typical experiment, a solution of the oxime (1 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a well stirred mixture of the dipolarophile (3 mmol), Et_3N (0.1 ml), CH_2Cl_2 (30 ml) and 8% aq. NaOCl (15 ml) at 0°C. After 2 h TLC indicated complete consumption of the oxime, and the reaction was then worked up and the products separated by chromatography. To test the efficiency of nitrile oxide formation a reaction was first carried out in the absence of a dipolarophile. Under these conditions glucose oxime **5** gave diglucopyranosylfuroxan **6**[13,14] (88%), which was identified from its spectroscopic properties (Table 1, entry 1, Scheme 2). In both the ^1H and ^{13}C NMR spectra there are distinct and independent sets of signals for the two glucosyl fragments, and in the carbon spectrum peaks are observed at 111.6 (C-3) and 153.4 (C-4) ppm, which are characteristic of the 1,2,5-oxadiazole ring.[15] Further evidence is provided by the mass spectrum which shows, in addition to the parent ion, a significant peak at M–60 corresponding to loss of N_2O_2; this mode of fragmentation is typical for furoxans.[15] It is well established[16] that nitrile oxides readily dimerise to furoxans, and isolation of compound **6** provides unambiguous evidence for efficient generation of the nitrile oxide **7**. The oximes derived form D-galactose and D-xylose reacted similarly affording the corresponding furoxans (Table 1, entries 2 and 3). The pyranosylfuroxans are of interest in their own right, and they can be regarded as *C*-disaccharides with functionalised ethylene bridges between the two anomeric positions.

Generating nitrile oxide **7** in the presence of an excess of methylenecyclohexane (1:5) afforded a mixture of furoxan **6** (53%) and the isoxazoline **8** (32%) resulting from regiospecific cycloaddition to the alkene. The more reactive dipolarophiles styrene and norbornene afforded correspondingly greater yields of cycloadducts **9** (53%) and **10** (76%), respectively (Table 1, entries 6 and 7).

The second method for generating nitrile oxide **7** involved initial conversion of oxime **5** to the corresponding hydroximoyl chloride **11**. This was achieved by bubbling chlorine through a solution of the oxime (1 mmol) in CH_2Cl_2 (5 ml) at −78°C, and allowing the mixture to warm to room temperature. After stirring for 16 h the solvent was removed in vacuo to yield **11**

Table 1. Generation and reactions of pyranosyl nitrile oxides



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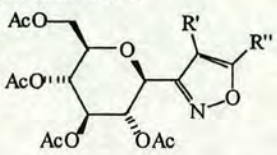
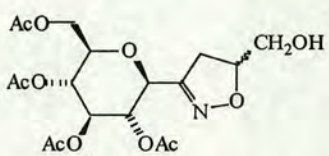


12 R' = R'' = CO_2Me
13 R' = H, R'' = CO_2Et
14 R' = CO_2Et, R'' = H



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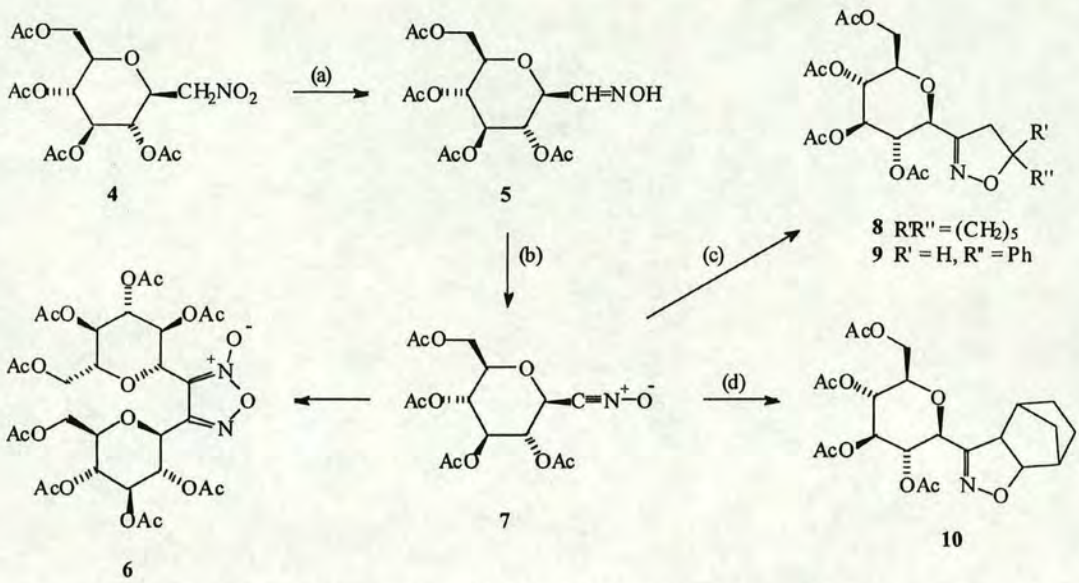
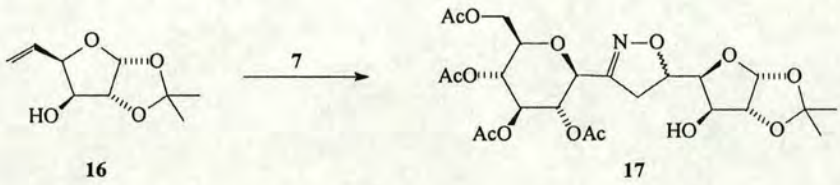
Entry	Nitrile oxide	Method[a]	Dipolarophile	Cycloadduct	Yield/% (d.r.)	Furoxan yield/%
1	D-Glc	A/B	None	–		88/96
2	D-Gal	A	None	–		90
3	D-Xyl	A	None	–		89
4	D-Man	B	None	–		95
5	D-Glc	A	Methylenecyclohexane	**8**	32	53
6	D-Glc	A	CH_2=CHPh	**9**	53 (55:45)	21
7	D-Glc	A	Norbornene	**10**	76 (61:39)	5
8	D-Man	A/B	CH_2=CHPh		85 (53:47)/95 (56:44)	Traces
9	D-Glc	B	$MeO_2C{\equiv}CO_2Me$	**12**	98	6
10	D-Glc	B	$HC{\equiv}CCO_2Et$	**13**+**14**	69 (85:15)[b]	15
11	D-Man	B	CH_2=$CHCH_2OH$	**15**	30	14
12	D-Glc	B	**16**	**17**	40 (72:28)	26
13	D-Gal	B	**16**		36 (75:25)	33

[a] (A) RCH=NOH+aq. NaOCl; (B) RCCl=NOH+Et_3N.
[b] Ratio of regioisomers **13** and **14**.



Scheme 2. *Reagents*: (a) $SnCl_2$/PhSH/Et_3N, THF; (b) aq. $NaOCl_2$ CH_2Cl_2; (c) methylenecyclohexane or styrene; (d) norbornene.



Scheme 3.

(90%) as a white solid which was recrystallised from hexane/Et_2O. Similar yields (90–95%) were obtained for the hydroximoyl chlorides[14] derived from the D-Gal, D-Man and D-Xyl. The nitrile oxides were then generated from the hydroximoyl chlorides by base-mediated dehydrochlorination. Typically, the hydroximoyl chloride (1 mmol) and the dipolarophile (5 mmol) were dissolved in dry Et_2O (20 ml) and Et_3N (1.1 mmol) in dry CH_2Cl_2 (40 ml) added at 0°C via a syringe over 24 h. The solvent was then removed in vacuo and the products separated by chromatography. Improved yields were achieved by this method, which also allowed a wider range of dipolarophiles to be employed. Representative examples are shown in Table 1, entries 8–13, Scheme 3. The formation of **15** from allyl alcohol and *C*-disaccharide precursor[1c,5] **17** from D-Glc-derived alkene **16** represent examples of isoxazolines which could not be prepared directly from the nitromethyl compound by the Mukaiyama method.[5] The nitrile oxide derived from D-Gal reacted similarly (Table 1, entry 13). Dipyranosylfuroxans were also readily prepared by this approach (Table 1, entries 1 and 4).

In conclusion, hypochlorite oxidation of pyranose-1-carbaldoximes and base-induced dehydrochlorination of the corresponding hydroximoyl chlorides provide effective means of generating pyranosyl nitrile oxides suitable for the synthesis of a range of *C*-glycosides. This approach is complementary to the current literature procedure based on isocyanate-mediated dehydration of pyranosylnitromethanes, and also provides easy access to novel dipyranosylfuroxans.

Acknowledgements

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TETRAHEDRON

3,4-Dipyranosyl-1,2,5-oxadiazole 2-oxides: synthesis and X-ray structure

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Abstract—3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (**7**) has been synthesised from D-mannose by a route involving as the key step dimerisation of mannopyranosyl nitrile oxide **2**. Three methods were used for the generation of the nitrile oxide: isocyanate-mediated dehydration of nitromethylmannose derivative **4**, treatment of aldoxime **5** with aq. hypochlorite, and base-induced dehydrochlorination of hydroximoyl chloride **6**. D-Gluco, D-galacto, D-xylo, and L-fucopyranosyl analogues **8**–**11** were prepared similarly. The structure of D-mannose-derived 1,2,5-oxadiazole 2-oxide **7** was established by X-ray crystallography.

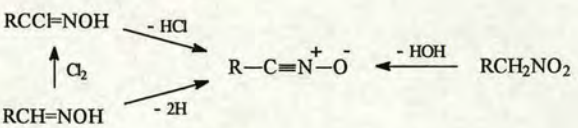
1. Introduction

1,2,5-Oxadiazole 2-oxides (furoxans, **1**) have been known since 1850s and much attention has been paid to structure determination, development of preparative methods, and examining their reactions.[1–3] A wide variety of substituents can be accommodated at the 3- and 4-positions, including alkyl, aryl, amino, halogeno, nitro and thio groups. To date, however, there have been few examples of carbohydrate-substituted furoxans.[4] While investigating synthetic routes to *C*-glycosides and carbon-linked disaccharides (*C*-disaccharides), we have sought novel methods for forming functionalised carbon bridges between pyranose rings, and now report that furoxans bearing pyranosyl substituents at both the 3- and 4-positions can readily be prepared in two steps from the parent monosaccharide.

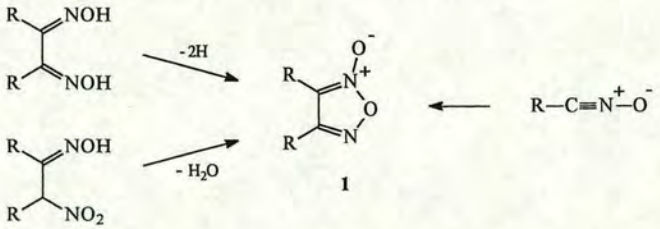
2. Results and discussion

The furoxan ring can be constructed by various methods,[1–3] the most synthetically useful of which are: the oxidative cyclisation of 1,2-dioximes, the dehydration of α-nitroketoximes and, for symmetrically substituted furoxans, the dimerisation of nitrile oxides (Scheme 1). As suitably substituted carbohydrate dioxime and nitroketoxime precursors are not readily available we selected the nitrile oxide dimerisation approach.

Nitrile oxides have been identified as intermediates in various reactions,[5] and of these three provide synthetically useful methods of generation (Scheme 2). Hydroximoyl chlorides (RCCl=NOH), which can be prepared from the parent aldoxime using chlorine, *N*-chlorosuccinimide, or nitrosyl chloride, undergo facile dehydrochlorination to the



Scheme 2.



Scheme 1.

Keywords: nitrile oxides; *C*-glycosides, pyranosylcarbaldoximes; pyranosylnitromethanes; X-ray crystallography.

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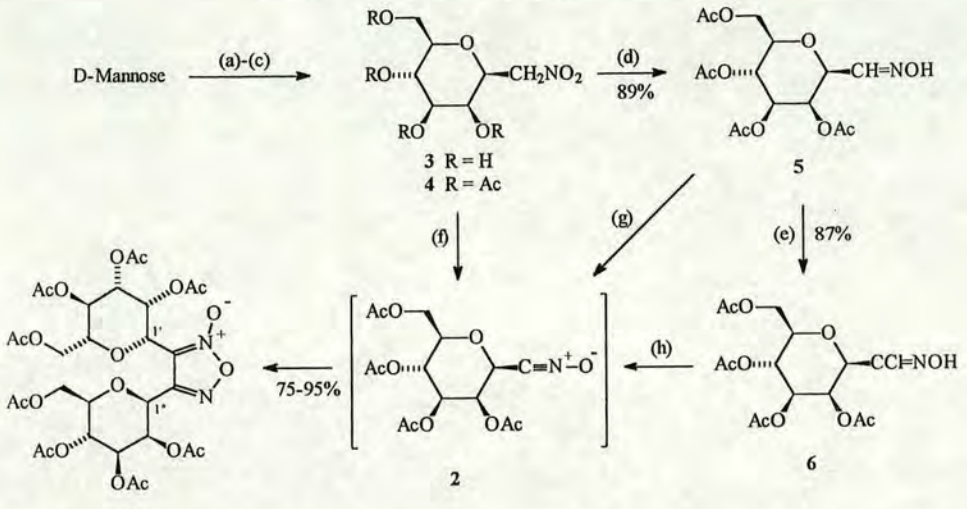


Scheme 3. *Reagents*: (a) $MeNO_2/NaOMe$, MeOH; (b) H_2O, reflux; (c) Ac_2O/CF_3SO_3H; (d) $SnCl_2/PhSH/Et_3N$, THF; (e) Cl_2, CH_2Cl_2; (f) TDI/Et_3N, PhMe, reflux, quench with $H_2NCH_2CH_2NH_2$; (g) aq NaOCl, CH_2Cl_2; (h) Et_3N, Et_2O.

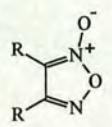
nitrile oxide in the presence of triethylamine; in the absence of base the nitrile oxide may be released by thermolysis in an inert solvent such as toluene.[6] There are also several one-pot methods[7,8] for generation of nitrile oxides from aldoximes including treatment with Chloramine-T or aq. NaOCl/CH_2Cl_2. The third approach, which was originally reported by Mukaiyama and Hoshino,[9] involves dehydration of the corresponding nitromethyl compound (RCH_2NO_2) with phenyl isocyanate; alternative dehydrating agents include $POCl_3$,[10] TsOH,[11] $ClCO_2Me$[12] and $PhSO_2Cl$.[13]

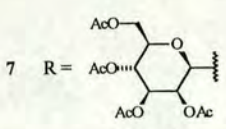
For the present work the choice of method is determined by the accessibility of the precursors. We initially considered a conventional approach to pyranose-1-carbaldoximes—and hence to the corresponding hydroximoyl chlorides—via oximation of *C*-pyranosyl aldehydes. The literature routes[14–16] to the aldehydes, however, all require several stages, some of which need expensive reagents and/or forcing conditions, and the products are prone to oxidation and hydration. We therefore selected pyranosylnitromethanes (2,6-anhydro-1-deoxy-1-nitroalditols) as the sources of the target pyranosyl nitrile oxides. These can readily be prepared[17] from the parent monosaccharide by base-catalysed addition of nitromethane (the Fischer–Sowden reaction). Subsequent reduction to the aldoximes, followed by chlorination should then afford the corresponding hydroximoyl chlorides. This sequence can thus provide access to all three potential precursors of the pyranosyl nitrile oxides. These approaches are illustrated in Scheme 3 for generation of nitrile oxide **2** derived from D-mannose.

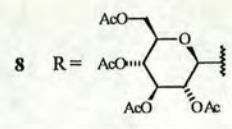
D-Mannose was converted into β-D-mannopyranosylnitromethane (**3**) using the general procedure of Köll et al.[17] which involves reaction with nitromethane and sodium methoxide in methanol, followed by heating the resulting adduct to achieve dehydration and cyclisation. As an isocyanate was to be used as the dehydrating agent it was necessary to protect all free hydroxyl groups, and compound **3** was therefore converted into its peracetate derivative **4** using $Ac_2O/MeSO_3H$. The aldoxime **5** was prepared from the nitromethyl compound by reduction with $SnCl_2/PhSH/Et_3N$. We have found that this protocol, which is based on a report by Bartra et al.,[18] and depends on the reducing ability of the stannate species $(PhS)_3Sn^-$, is an effective and general method for reducing nitromethyl monosaccharides. Hydroximoyl chloride **6**, the third potential precursor for nitrile oxide **2**, was prepared by chlorination of oxime **5**. Although direct chlorination of aldoximes can be a capricious reaction, and alternative reagents such as NCS and NOCl are often used,[5] it proved to be very successful in this case. Bubbling chlorine through a solution of the oxime in CH_2Cl_2 at −78°C resulted in a colour change (colourless→blue→green) attributable to formation of the nitroso tautomer of the hydroximoyl chloride, and work-up of the reaction mixture afforded the desired product **6** as a white solid in 87% yield. Complete aldoxime to hydroximoyl chloride conversion is evident from the NMR spectra. In the proton spectrum the 1-H signal at 7.37 ppm for the aldoxime is absent and the 2-H signal simplifies from a doublet of doublets to a doublet (1.9 Hz); and in the carbon spectrum the aldoxime CH peak at 146.1 ppm is replaced by a new quaternary carbon signal at 134.6 ppm. Although the starting material was a mixture of *E*- and *Z*-oximes, NMR spectroscopy showed the product to be a single isomer. The same approach was used to prepare the aldoximes and hydroximoyl chlorides from D-glucose, D-galactose, D-xylose and L-fucose.

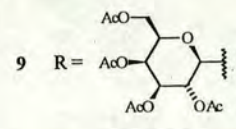
The nitrile oxide **2** was first generated by heating under reflux a toluene solution of nitromethyl compound **4** and tolylene diisocyanate (TDI) (3 equiv.) with a catalytic amount of triethylamine. On completion the reaction was quenched by addition of 1,2-diaminoethane to remove excess isocyanate, and the solvent evaporated to afford the nitrile oxide dimer 3,4-di-(tetra-*O*-acetyl-β-D-mannopyranosyl)furoxan (**7**) as a crystalline solid in 90% yield (Table 1, entry 1). TDI was used for the dehydration in place of the traditional phenyl isocyanate for ease of work-up, as the by-product is then a polymeric urea which is readily separated by filtration.[19] The second approach to the nitrile

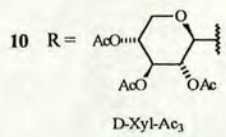
Table 1. 3,4-Dipyranosylfuroxans

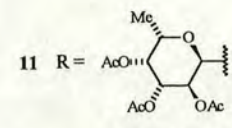


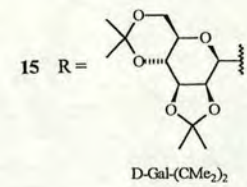












Entry	Furoxans	R	Method[a]	Yield (%)
1	**7**	D-Man-Ac_4	A	90
2	**7**	D-Man-Ac_4	B	75
3	**7**	D-Man-Ac_4	C	95
4	**8**	D-Glc-Ac_4	B	88
5	**8**	D-Glc-Ac_4	C	96
6	**9**	D-Gal-Ac_4	B	90
7	**10**	D-Xyl-Ac_3	A	81
8	**10**	D-Xyl-Ac_3	B	89
9	**11**	L-Fuc-Ac_3	A	79
10	**15**	D-Man-$(CMe_2)_2$	A	92

[a] Method A: RCH_2NO_2/TDI; Method B: RCH=NOH/NaOCl; Method C: RCCl=NOH/Et_3N.

oxide involved oxidation of the aldoxime with hypochlorite using the two-phase procedure reported by Lee et al.[8] A solution of oxime **5** in dichloromethane was added dropwise to a stirred mixture of aqueous sodium hypochlorite and dichloromethane containing a catalytic amount of triethylamine. Separation of the phases and work-up of the organic layer afforded furoxan **7** in 75% yield (Table 1, entry 2). Finally the nitrile oxide was generated by base-mediated dehydrochlorination of hydroximoyl chloride **6**. A solution of triethylamine (1.1 equiv.) in Et_2O was added to a solution of **6** (1.0 equiv.) in Et_2O at 0°C and the mixture stirred at room temperature for 16 h. After filtration and washing with water to remove triethylamine hydrochloride, the solution was concentrated to afford furoxan **7** (95%) (Table 1, entry 3).

D-Glucose, D-galactose, D-xylose and L-fucose-derived furoxans **8**–**11** were prepared similarly (Table 1, entries 4–9) and in all cases the yields were very good (75–96%). The products were identified by their analytical and spectroscopic properties. ^{13}C NMR spectroscopy is of particular value in identifying these compounds. In addition to resonances attributable to the two peracetylpyranosyl substitutents, there are characteristic peaks in the ranges 110.5–111.6 (C-3) and 152.7–153.4 ppm (C-4) for the carbons of the oxadiazole ring. These values are typical for unstrained furoxans.[2] In the proton NMR spectrum of dimannosylfuroxan **7** in $CDCl_3$ the two non-equivalent pyranosyl substituents lead to overlapping and only partially resolved signals. There are, however, distinct doublets for protons H(1′) and H(1″), which are attached to the carbons adjacent to C(3) and C(4), respectively, of the furoxan ring; the observed 1 Hz couplings to H(2′)/H(2″) are in accord with the β-D-manno configuration of the pyranoid rings. The higher chemical shift doublet was assigned to H(1″) by analogy with data reported for other dialkylfuroxans.[1,2] A fuller analysis was performed for diglucosylfuroxan **8**. In $CDCl_3$ the spectra were again poorly resolved and alternative solvents were therefore examined, including C_6D_6 and CD_3COCD_3. In all solvents the expected 10 Hz doublet signals are observed for protons H(1′) and H(1″). Acetone-d_6 provided the best overall resolution and a near complete proton and carbon assignment was achieved from COSY and HETCOR spectra. Identical proton–proton ^3J couplings are observed for the two pyranoid frameworks [H(1)–H(2) 10.0, H(2)–H(3) 9.3, H(3)–H(4) 9.3, H(4)–H(5) 10.1 Hz]; these values are typical of *C*-glucosides. The separation of the H(1) signals proved to be solvent dependent ($\Delta\delta_H$ 0.01 ppm in $CDCl_3$, 0.06 ppm in CD_3COCD_3, 0.14 ppm in C_6D_6–$CDCl_3$). Smaller $\Delta\delta$ values are found for the ring protons H(2)–H(5). In the ^{13}C spectra the C(1) signals are well separated ($\Delta\delta_C$ 2.1 ppm in CD_3COCD_3), but the remaining carbon signals are near equivalent ($\Delta\delta_C \leq 0.1$ ppm). Their mass spectra are also typical of this class of heterocycle;[1,2] in addition to the molecular ion peak $(M+1)^+$ in the FAB spectrum, there is a

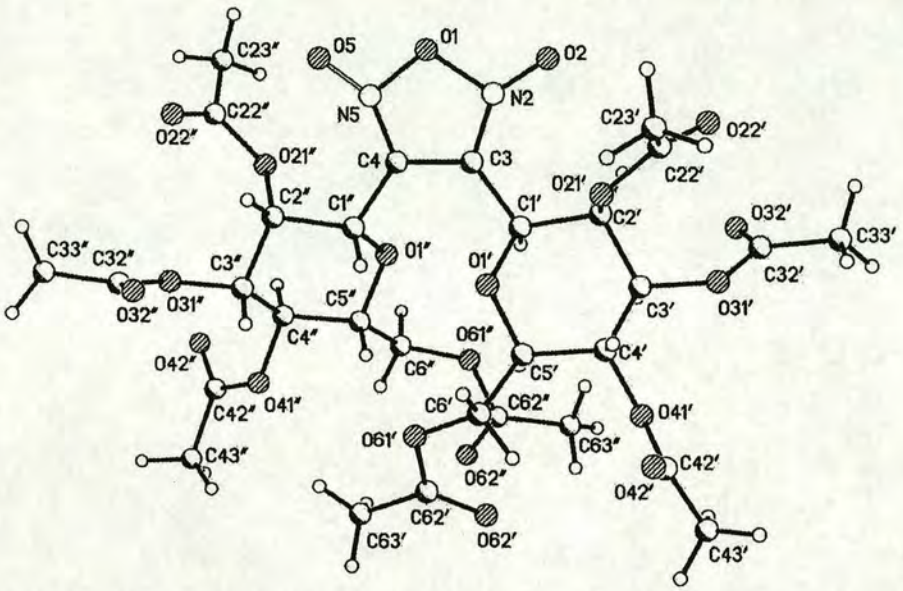


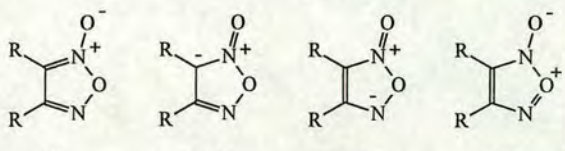
Figure 1. Structure of **7**. O2 and O5 are disordered in the ratio 0.85:0.15.

Table 2. Selected bond lengths, bond angles and torsion angles for furoxan **7**

Bond lengths (Å)	Bond angles (°)	Torsion angles (°)
O(1)–N(2) 1.465(7)	O(1)–N(2)–C(3) 105.1(5)	O(1)–N(2)–C(3)–C(4) 0.16
N(2)–C(3) 1.319(8)	N(2)–C(3)–C(4) 108.3(5)	N(2)–C(3)–C(4)–N(5) 0.29
C(3)–C(4) 1.418(9)	C(3)–C(4)–N(5) 110.6(5)	C(3)–C(4)–N(5)–O(1) −0.68
C(4)–N(5) 1.309(7)	C(4)–N(5)–O(1) 107.3(5)	C(4)–N(5)–O(1)–N(2) 0.76
N(5)–O(1) 1.355(8)	N(5)–O(1)–N(2) 108.7(4)	N(5)–O(1)–N(2)–C(3) −0.57
N(2)–O(2) 1.180(7)	O(1)–N(2)–O(2) 115.2(5)	O(1)–N(2)–C(3)–C(1′) 177.51
	C(3)–N(2)–O(2) 139.7(6)	O(2)–N(2)–C(3)–C(1′) −1.19
		O(1)–N(5)–C(4)–C(1″) −179.63

distinctive fragment peak at $(M-59)^+$ corresponding to loss of N_2O_2, whereas the peak due to loss of O, which is usually present for heterocyclic *N*-oxides, is weak.

The structure of D-mannose-derived furoxan **7** was confirmed by X-ray crystallography (Fig. 1). A noteworthy feature of the crystal structure is disorder in the furoxan moiety, with the *N*-oxide substituent being located at the 2- and 5-positions in the ratio 0.85:0.15. Disorder of this type has also been reported[20,21] for diphenyl- and tetramethylene-furoxans [**1**, R=Ph, $(CH_2)_4$] and some norbornane-fused furoxans.[22] Selected bond lengths, bond angles and torsion angles for the furoxan ring system are given in Table 2. The atoms of the furoxan unit O(1), N(2), C(3), C(4), N(5), O(2) are near planar (maximum deviation 0.004 Å), as are the atoms C(1′), C(3), C(4), C(1″) linking the oxadiazole to the two pyranoid substituents. The bond lengths are typical of furoxans[2] and indicate π-electron delocalisation over all six atoms with the exocyclic oxygen attached to N(2) causing significant distortion of the oxadiazole ring. Of particular note is the long O(1)–N(2) and short N(2)–O(2) bonds. C(3)–C(4) is also shortened corresponding to partial double bond character, and N(2)–C(3) is longer than C(4)–N(5), consistent with contributions from **12b–12d** to the resonance hybrid. The bond angles of the C=NO_2 unit are also typical of 3,4-disubstituted furoxans, with O(2)–N(2)–C(3) significantly larger than O(2)–N(2)–O(1) [139.7° cf 115.2°].



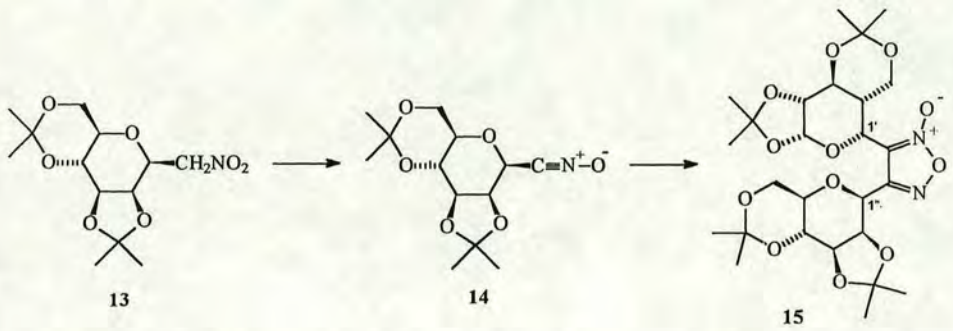
12a **12b** **12c** **12d**

The Cramer and Pople[23] puckering parameters for the two pyranoid rings are given in Table 3. Ring A attached to C-3 of the furoxan has 98% of the puckering of an ideal cyclohexane chair conformation, with Q=0.596 Å and θ=175.7° compared with Q=0.630 Å and θ=180° for the ideal chair. Similarly for ring B attached to C-4 with

Table 3. Cremer and Pople puckering parameters for pyranoid rings of furoxan **7**

Ring	Atoms	Q (Å)	θ (°)	ϕ (°)
A	O(1′)–C(5′)–C(4′)–C(3′)–C(2′)–C(1′)	0.596	175.7	105.1
B	O(1″)–C(5″)–C(4″)–C(3″)–C(2″)–C(1″)	0.593	176.7	213.7

Ref. 23.



Scheme 4.

Q=0.593 Å and θ=176.7°. Such values are typical of pyranoid rings.[24]

All the dipyranosylfuroxans described so far have been prepared as their peracetate derivatives using the acetylated nitromethylpyranose as the starting material. In order to widen the range of protecting groups, and thus ultimately increase the scope for transformations that might be accomplished on the resulting furoxans, we investigated diisopropylidene-mannose analogue **13** as a possible precursor of nitrile oxide **14** (Scheme 4). Compound **13** was prepared from β-D-mannopyranosylnitromethane (**3**) by treatment with 2-methoxypropene/TsOH/$CaSO_4$/DME as previously reported.[24] The nitrile oxide was then generated from the nitromethyl compound **13** in the usual way using TDI/Et_3N, and from the reaction mixture was isolated the nitrile oxide dimer **15** (92%), which was identified from its NMR and mass spectra. The ^1H NMR signals for the pyranoid ring protons were best resolved in $CDCl_3$ and a full analysis was possible from the 600 MHz COSY and 1D-TOCSY spectra. The signals for H(1′) and H(1″) are well separated ($\Delta\delta_H$ 0.16 ppm) and show the expected small couplings (2.5 Hz) to H(2′)/H(2″). As expected, the presence of the dioxolane ring fused at C(2)/C(3) results in some distortion of the regular $^4C_1$ conformation, as evidenced by the proton–proton ^3J couplings [H(1)–H(2) 2.6, H(2)–H(3) 5.2, H(3)–H(4) 7.9, H(4)–H(5) 10.1 Hz]. The chemical shifts for the isopropylidene ketal carbons provide definitive evidence for the presence of both 1,3-dioxane and 1,3-di-oxolane rings attached to both pyranosyl substituents. For the 1,3-dioxane units protecting O(4)/O(6) there are characteristic signals for the ketal carbons at 99.9 and 100.0 ppm and for the isopropylidene methyl carbons at 18.7, 18.7, 28.7 and 28.9 ppm. Corresponding signals for the dioxolane unit protecting O(2)/O(3) are observed at 110.4, 110.5 (ketal carbons) and 26.4, 27.3, 28.3, 28.4 ppm (methyl carbons). Such values are typical[25] of 2,2-dimethyl-1,3-di-oxolanes and 2,2-dimethyl-1,3-dioxanes, respectively (Scheme 4).

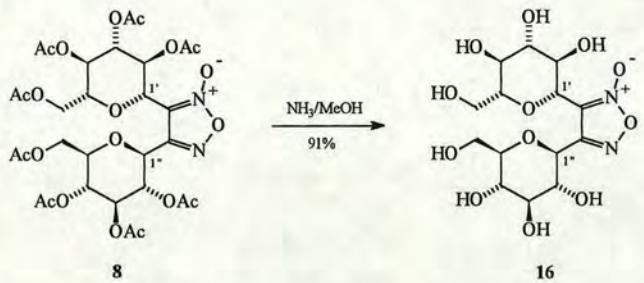
Finally, the unprotected 3,4-di-D-glucosyl-furoxan **16** was prepared by treatment of the octa-acetyl derivative **8** with NH_3/MeOH (Scheme 5). The product was identified from its spectroscopic properties. In the ^{13}C NMR spectrum in D_2O there are diagnostic peaks for the oxadiazole ring carbons C(3) and C(4) at 115.4 and 156.0 ppm, respectively, which are 3–4 ppm higher than those found for the peracetyl analogue in acetone-d_6. The glucosyl H(1′)/H(1″) doublet signals in the proton spectrum are well separated at 4.56 and 4.60 ppm, and both show the expected trans-diaxial 10 Hz coupling to H(2′)/H(2″). The product, which was isolated in high yield (91%), represents a rare example of a water-soluble furoxan.

In conclusion, dipyranosylfuroxans can be synthesised in good yield from the parent monosaccharide. Of the three procedures examined the two-step route involving conversion of the monosaccharide to a suitably protected nitromethylpyranose, followed by dehydration to the pyranosyl nitrile oxide, is in most cases the most efficient. As furoxan rings are readily reduced,[1,2] e.g. to 1,2,5-oxadiazoles (furazans) and 1,2-dioximes, there should be further scope for the preparation of novel carbon-bridged disaccharides.

3. Experimental

3.1. General

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. Microanalyses were



Scheme 5.

obtained using a Perkin–Elmer 2400 instrument. Optical rotations were measured at 21°C on a Perkin–Elmer 141 polarimeter using 1.8 ml of filtered solution. The ^{1}H and ^{13}C NMR spectra were recorded with Brucker WP200SY, AX250, WH360 or Varian VXR600 spectrometers on solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard. Positive-ion FAB and high resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Infrared spectra were recorded as films or nujol mulls using a Perkin–Elmer 781 spectrometer. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC; detection was by UV or sulfuric acid charring. Dry flash chromatography was carried out using Kieselgel GF_{254} and eluted under water pump vacuum.

3.2. Pyranosylnitromethanes

2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosylnitromethane (**4**) was prepared from D-mannose by reaction with $MeNO_2$/NaOMe/MeOH and acetylation of the resulting β-D-mannopyranosyl-nitromethane (**3**) as previously reported.[17] 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-nitromethane, 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-nitromethane, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-nitromethane, and 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl-nitromethane were prepared similarly from D-glucose, D-galactose, D-xylose, and L-fucose, respectively. 2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosylnitromethane (**13**) was synthesised from β-D-mannopyranosylnitro-methane by treatment with 2-methoxypropene/TsOH/$CaSO_4$/DME as described in the literature.[24]

3.3. General procedure for the synthesis of the pyranosylformaldoximes

Triethylamine (0.2 ml, 1.5 mmol) and thiophenol (0.14 ml, 1.35 mmol) were added to a solution of tin(II) chloride (100 mg, 0.45 mmol) in dry THF (6 ml) under nitrogen at 0°C. To the resulting solution was added a solution of the pyranosylnitromethane (0.3 mmol) and the mixture stirred for 16 h. After removal of the solvent in vacuo, the residue was washed with hexane to remove excess thiophenol, and the product separated by dry-flash chromatography (silica, hexane/Et_2O gradient elution) to afford compound as a mixture of *E*- and *Z*-isomers. The isomer ratio was determined by comparison of the 1-H peaks at ~7.3 and ~6.7 ppm.

3.3.1. 2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosylformaldoxime (5). 89%; white solid; mp 154–156°C (from hexane/Et_2O) (lit.[26] 152–154°C); *E*/*Z*=2.3:1.

3.3.2. Tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime. 76%; mp 139–140°C (from hexane/Et_2O) (lit.[26] 155–157°C); *E*/*Z*=5:1.

3.3.3. Tetra-*O*-acetyl-β-D-galactopyranosylformaldoxime. 89%; mp 184–185°C (from hexane/Et_2O) (lit.[26] 170–172°C); *E*/*Z*=9:1.

3.3.4. Tri-*O*-acetyl-β-D-xylopyranosylformaldoxime. 83%, mp 135–137°C (from hexane/Et_2O) (lit.[26] 160–163°C).

3.3.5. Tri-*O*-acetyl-β-L-fucopyranosylformaldoxime. 90%; mp 37–39°C; *E*-isomer: $[\alpha]_D^{18}=-22$ (*c*=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 3311 (OH), 1744 (C=O); δ_H (250 MHz, $CDCl_3$) 1.17, (3H, d, 7-H), 1.97, 2.00, 2.17, (9H, 3s, 3×$COCH_3$), 3.83 (1H, td, 6-H), 3.98 (1H, dd, 2-H), 5.07, (1H, dd, 4-H), 5.13–5.27, (2H, m, 3-H and 5-H), 7.33, (1H, d, 1H), 8.54, (1H broad s, NOH); *J*(*x*–*y*, Hz) 1–2 6.9, 2–3 9.7, 3–4 10.2, 4–5 3.3, 5–6 1.0, 6–7 6.4; δ_C (63 MHz, $CDCl_3$) 16.2 (C-7), 20.5, 20.6 (3×$COCH_3$), 66.8, 70.4, 71.7, 72.9, 75.9, (C-2–C-6), 147.2 (C-1), 169.9, 170.1, 170.6 (3×$COCH_3$); HRMS (FAB) Found: M^++1, 318.1180. $C_{13}H_{20}NO_8$ requires 318.11889; *E*/*Z*=7:1.

3.4. General procedure for the synthesis of the hydroximoyl chlorides

Dry chlorine gas was bubbled through a solution of the pyranosylformaldoxime (ca 1 mmol) in dry dichloro-methane (15 ml) at −78°C until the colour changed from blue to green. On warming to room temperature the colour faded and the solvent was removed in vacuo to afford an oil. The product was dissolved in ca 1 ml of dichloromethane and allowed to crystallise.

3.4.1. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*galacto*-heptitol (6). 87%; white powder; mp 102–103°C; $[\alpha]_D^{18}=111.8$ (*c*=0.7, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 3503 (OH), 1744 (C=O); δ_H (250 MHz, $CDCl_3$) 1.98, 2.04, 2.09, 2.12 (12H, 4s, 4×$COCH_3$), 3.73, (1H, ddd, 6-H), 4.23 (1H, dd, 7a-H), 4.29 (1H, dd, 7b-H), 5.06–5.33 (3H, m, 2-H, 4-H, 5-H) 5.73 (1H, t, 3-H), 8.80 (1H, broad s, NOH); *J*(*x*–*y*, Hz) 2–3 1.9, 3–4 3.3, 4–5 nd, 5–6 9.8, 6–7a 2.5, 6–7b 5.6, 7a–7b 12.3; δ_C (90 MHz, $CDCl_3$) 20.38, 20.44, 20.55 (4×$COCH_3$), 62.4 (C-7), 65.5, 67.7, 71.6, 76.5, 77.1 (C-2–C-6), 134.6 (C-1) 169.4, 169.5, 169.9, 170.2 (4×$COCH_3$); HRMS (FAB) Found: M^++1, 410.08545. $C_{15}H_{21}NO_{10}^{35}Cl$ requires 410.08540. Found: M^++1, 412.06859. $C_{15}H_{21}NO_{10}^{37}Cl$ requires 412.08245.

3.4.2. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-*glycero*-D-*gulo*-heptitol. 90%; white needles; mp 157–159°C (from CH_2Cl_2); ν_{max} (cm^{-1}, Nujol) 3311 (OH), 1747 (C=O); $[\alpha]_D^{18}=-5.0$ (*c*=1.0, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.97, 2.00, 2.03, 2.07 (12H, 4s, 4×$COCH_3$), 3.80 (1H, dd, 6-H), 4.14 (1H, dd, 7a-H), 4.23 (1H, dd, 7b-H), 4.31 (1H, d, 2-H), 5.14, 5.26, 5.36 (3H, 3dd, 3-H, 4-H, 5-H), 8.93 (1H, br s, NOH); *J*(*x*–*y*, Hz) 2–3 9.6, 3–4 nd, 4–5 nd, 5–6 9.8, 6–7a 2.4, 6–7b 4.6, 7a–7b 12.5; δ_C (63 MHz, $CDCl_3$) 20.4, 20.5, 20.5, 20.6 (4×$COCH_3$), 61.8 (C-7), 67.8, 68.8, 73.7, 75.7, 78.3 (C-2–C-6), 136.2 (C-1), 169.2, 169.5, 170.5, 170.8 (4×$COCH_3$); HRMS (FAB) Found: M^++1, 410.08565. $C_{15}H_{21}NO_{10}^{35}Cl$ requires 410.08540. Found: M^++1, 412.08226. $C_{15}H_{21}NO_{10}^{37}Cl$ requires 412.08245.

3.5. Synthesis of the dipyranosylfuroxans (3,4-dipyranosyl-1,2,5-oxadiazole 2-oxides)

The furoxans were prepared by dimerisation of the corresponding nitrile oxides, which were generated either by dehydration of the pyranosylnitromethane (Method A), or dehydrogenation of the pyranosylformaldoxime (Method

B), or dehydrochlorination of the pyranosyl hydroximoyl chloride (Method C). The yields are shown in Table 1.

Method A. To a solution of the pyranosylnitromethane (0.5 mmol, 1 equiv.) in dry toluene (20 ml) under nitrogen was added triethylamine (0.1–0.2 ml) and tolylene diisocyanate (3 equiv.), and the mixture heated under reflux for 7 days. After cooling to 0°C 1,2-diaminoethane (3 equiv.) was added dropwise with stirring. After 1 h the mixture was filtered through a celite pad to remove the precipitated polymeric urea. The pad was washed with toluene and chloroform and the combined organic layers evaporated to afford the product which was purified by chromatography and/or recrystallisation.

Method B. Aqueous sodium hypochlorite (5%, 16.2 mmol, 60 equiv.) was added dropwise to a stirred solution of the pyranosylformaldoxime (0.26 mmol, 1 equiv.) in H_2O/CH_2Cl_2 (1:1, 20 ml). After stirring overnight the organic layer was separated and the aqueous layer extracted with chloroform (3×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to yield the product, which was recrystallised from the appropriate solvent.

Method C. To a solution of the pyransoyl hydroximoyl chloride (0.22 mmol, 1 equiv.) in dry Et_2O (10 ml) triethylamine (0.25 mmol, 1.1 equiv.) was added dropwise via a syringe and the solution left to stir overnight. The mixture was then poured into water, the organic layer separated and the aqueous layer extracted with chloroform (3×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to yield the product, which was purified by recrystallisation.

3.5.1. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (7). White needles, mp 213–215°C (from EtOH) (Found: C, 47.9; H, 5.0, N, 3.8. $C_{30}H_{38}N_2O_{20}$ requires C, 48.2; H, 5.1, N, 3.7); $[\alpha]_D^{18}=-14.0$ (c=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1743 (C=O), 1606 (C=N); δ_H (250 MHz, $CDCl_3$) 1.93, 1.93, 1.96, 2.02, 2.03, 2.05, 2.05, 2.06, 2.07, 2.11 (24H, 8s, 8×$COCH_3$), 3.80–3.94 (2H, m, 5′-H, 5″-H), 4.17–4.36 (4H, m, 6′a-H, 6′b-H, 6″a-H, 6″b-H), 4.93 (1H, d, $J_{1'-2'}$ 0.9, 1′-H), 5.17 (1H, d, $J_{1''-2''}$ 1.0, 1″-H), 5.10–5.36 (4H, m, 2′-H, 2″-H, 4′-H, 4″-H), 5.68–5.74 (2H, m, 3′-H, 3″-H); δ_C (63 MHz, $CDCl_3$) 20.3, 20.3, 20.4, 20.4, 20.6, 20.6 (8×$COCH_3$), 62.1, 62.7 (C-6′, C-6″), 64.9, 65.4, 66.0, 67.3, 70.5, 71.0, 71.6, 76.8, 77.1 (C-1′, C-2′, C-3′, C-4′, C-5′, C-1″, C-2″, C-3″, C-4″, C-5″), 110.5 (C-3), 152.7 (C-4), 169.2, 169.3, 169.6, 169.7, 169.9, 170.2, 170.3 (8×$COCH_3$); m/z (FAB) 747 (M^++1), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 747.20920. $C_{30}H_{39}N_2O_{20}$ requires 747.20962. The structure of compound **7** was confirmed by X-ray crystallography.

3.5.2. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (8). White solid, mp 118–120°C (from Et_2O–hexane) (Found: C, 47.9; H, 5.0, N, 3.4. $C_{30}H_{38}N_2O_{20}$ requires C, 48.2; H, 5.1, N, 3.7); $[\alpha]_D^{18}=-40.4$ (c=0.74, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1747 (C=O), 1599 (C=N); δ_H (360 MHz, CD_3COCD_3) 1.94, 1.95, 2.00, 2.05, 2.06, 2.08, 2.14, 2.15 (24H, 8s, 8×$COCH_3$), 4.18–4.22 (2H, m, 6′b-H, 6″b-H), 4.27 (2H, m, 5′-H, 5″-H), 4.46–4.54 (2H, m, 6′a-H, 6″a-H), 5.16 (1H, d, 1′-H), 5.22 (1H, d, 1″-H), 5.33 (1H, dd, 4′-H), 5.36 (1H, dd, 4″-H), 5.53 (2H, dd, 3′-H, 3″-H), 5.64 (1H, dd, 2″-H), 5.65 (1H, dd, 2′-H); $J(x-y$, Hz) 1′2′ 10.0, 2′–3′ 9.3, 3′–4′ 9.3, 4′–5′ 9.3, 5′–6a′ nd, 5′–6a′ nd, 6a′–6b′ nd, 1″2″ 10.0, 2″–3″ 9.3, 3″–4″ 9.3, 4″–5″ 9.3, 5″–6a″ nd, 5″–6a″ nd, 6a″–6b″ nd; δ_C (63 MHz, CD_3COCD_3) 18.6, 18.7, 18.8, 18.8, 19.1, 19.1 (8×$COCH_3$), 60.9 (C-6′, C-6″), 66.9, 67.0 (C-4′, C-4″), 68.9, 69.0 (C-2′, C-2″), 69.6 (C-1′), 71.7 (C-1″), 72.6, 72.7 (C-3′, C-3″), 75.4, 75.5 (C-5′, C-5″), 111.6 (C-3), 153.4 (C-4), 168.0, 168.1, 168.6, 168.6, 169.2 (8×$COCH_3$); m/z (FAB) 747 (M^++1), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 747.20936. $C_{30}H_{39}N_2O_{20}$ requires 747.20962.

3.5.3. 3,4-Di(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2,5-oxadiazole 2-oxide (9). White solid, mp 167–168°C (from Et_2O–hexane); $[\alpha]_D^{18}=-6.4$ (c=0.14, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.96, 1.97, 1.98, 1.99, 2.03, 2.04, 2.21, 2.22 (24H, 8s, 8×$COCH_3$), 4.03–4.24 (6H, m), 4.79 (1H, d, $J_{1'-2'}$=10.0 Hz, 1′-H), 4.82 (1H, d, $J_{1''-2''}$=10.0 Hz, 1″-H), 5.12–5.19 (2H, m), 5.47–5.66 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.3, 20.4, 20.5 (8×$COCH_3$), 61.1 (C-6′, C-6″), 65.7, 66.7, 67.0, 67.1, 70.6, 71.5, 72.7, 75.0, 75.1 (C-1′-C-5′, C-1″-C-5″), 111.5 (C-3), 153.0 (C-4), 169.0, 169.3, 169.8, 169.9, 170.2 (8×$COCH_3$); m/z (FAB) 748 (M^++2), 687 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: (M−N_2O_2)$^+$+1, 687.21371. $C_{30}H_{39}O_{18}$ requires 687.21364.

3.5.4. 3,4-Di(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,5-oxadiazole 2-oxide (10). White solid; mp 190°C; $[\alpha]_D^{18}=-33$ (c=1.0, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1759 (C=O), 1600 (C=N); δ_H (250 MHz, $CDCl_3$) 1.94, 2.03, 2.06, 2.07, 2.07 (18H, 6s, 6×$COCH_3$), 3.40–3.52 (2H, m), 4.10–4.22 (1H, m), 4.29–4.38 (1H, m), 4.62 (2H, 2d, $J_{1'-2'}$=9.5 Hz, $J_{1''-2''}$=9.6 Hz, 1′-H, 1″-H), 5.00–5.10 (2H, m), 5.28–5.43 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.0, 20.3, 20.5 (6×$COCH_3$), 66.9, 66.9 (C-6′, C-6″), 68.3, 69.7, 70.2, 71.6, 72.3, 72.4, 73.9, 76.3 (C-1′-C-5′, C-1″-C-5″), 112.7 (C-3), 153.7 (C-4), 169.3, 169.5, 169.6, 169.8, 169.9 (6×$COCH_3$); m/z (FAB) 603 (M^++1), 543 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 603.17504. $C_{24}H_{33}N_2O_{16}$ requires 603.17518.

3.5.5. 3,4-Di(2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl)-1,2,5-oxadiazole 2-oxide (11). White solid; mp 213°C (from hexane–EtOAc); $[\alpha]_D^{18}=27.8$ (c=0.29, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.23–1.28 (6H, 2t, 2×CH_3), 2.01, 2.02, 2.03, 2.04, 2.26, 2.28 (18H, 6s, 6×$COCH_3$), 3.87–4.00 (2H, 2dd, 5′-H, 5″-H), 4.85 (2H, 2dd, 1′-H, 1″-H), 5.19 (2H, 2dd, 4′-H, 4″-H), 5.39 (2H, dd, 3′-H, 3″-H), 5.63 (2H, 2dd, 2′-H, 2″-H); $J(x-y$, Hz) 1′–2′ 10.1, 2′–3′ nd, 3′–4′ nd, 4′–5′ 1.0, 5′–6′ 6.4, 1″2″ 10.1, 2″–3″ nd, 3″–4″ nd, 4″–5″ 1.0, 5″–6″ 6.4; δ_C (63 MHz, $CDCl_3$) 16.7, 16.8 (2×CH_3), 20.8, 21.0, 21.1, 21.2 (6×$COCH_3$), 66.4, 67.0, 70.7, 70.7, 71.1, 72.4, 72.7, 72.9, 74.2, 74.3 (C-1′-C-5′, C-1″-C-5″), 112.5 (C-3), 153.8 (C-4), 169.7, 170.0, 170.5, 170.6, 170.9, 170.9 (6×$COCH_3$); m/z (FAB) 681 (M^++1), 571 [(M−N_2O_2)$^+$+1]; HRMS (FAB) Found: M^++1, 631.19732. $C_{26}H_{35}N_2O_{16}$ requires 631.19866.

3.5.6. 3,4-Di(2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide (15). White solid; mp 131–133°C (from hexane) (Found: C, 54.7; H, 6.8, N, 4.8. $C_{20}H_{38}N_2O_{12}$ requires C, 54.7; H, 6.7, N, 4.9);

$[\alpha]_D^{18}$=29.1 (c=0.23, $CHCl_3$); ν_{max} (cm^{-1}, Nujol) 1606 (C=N); δ_H (600 MHz, $CDCl_3$) 1.35, 1.37, 1.48, 1.48, 1.57, 1.58, 1.58, 1.64 (24H, 8s, 8×CCH_3), 3.28 (1H, dt, 5″-H), 3.33 (1H, dt, 5′-H), 3.73 (1H, t, 6ax′-H), 3.80 (1H, dd, 4′-H), 3.90 (1H, t, 6ax″-H), 3.97 (dd, 4″-H), 3.99 (1H, dd, 6eq″-H), 4.01 (1H, dd, 6eq′-H), 4.18 (1H, dd, 3″-H), 4.21 (1H, dd, 3′-H), 4.53 (1H, t, 2′-H), 4.54 (1H, t, 2″-H), 5.05 (H, d, 1′-H), 5.21 (1H, d, 1″-H); J(x–y, Hz) 1′–2′ 2.6, 2′–3′ 5.2, 3′–4′ 7.9, 4′–5′ 10.1, 5′–6ax′ 10.7, 5′–6eq′ 5.5, 6ax′–6eq′ 10.2, 1″–2″ 2.4, 2″–3″ 5.1, 3″–4″ 7.9, 4″–5″ 10.1, 5″–6ax″ 10.7, 5″–6eq″ 5.5, 6ax″–6eq″ 10.1; δ_H (600 MHz, CD_3COCD_3) 1.31, 1.32, 1.35, 1.36, 1.52, 1.53, 1.54, 1.56 (24H, 8s, 8×CCH_3), 3.39 (1H, dt, 5″-H), 3.48 (1H, dt, 5′-H), 3.82 (1H, t, 6ax″-H), 3.85–3.96 (5H, m, 4′-H, 4″-H, 6ax′-H, 6eq′-H, 6eq″-H), 4.19 (1H, dd, 3″-H), 4.28 (1H, dd, 3′-H), 4.64 (1H, dd, 2″-H), 4.68 (1H, dd, 2′-H), 5.31 (H, d, 1′-H), 5.46 (1H, d, 1″-H); J(x–y, Hz) 1′–2′ 2.7, 2′–3′ 5.3, 3′–4′ 7.9, 4′–5′ 10.0, 5′–6ax′ 10.0, 5′–eq′ 5.7, 6ax″–6eq″ nd, 1″–2″ 2.5, 2″–3″ 5.2, 3″–4″ 7.9, 4″–5″ 10.0, 5″–6ax″ 10.1, 5″–6eq″ 5.7, 6ax″–eq″ 10.7; δ_C (63 MHz, $CDCl_3$) 18.7, 18.7, 26.4, 27.3, 28.3, 28.4, 28.7, 28.9 (8×*C*CH_3), 61.5, 61.6, 71.1, 71.4, 72.3, 72.5, 72.6, 73.8, 75.4, 75.8 (C-1′–C-5′, C-1″–C-5″), 61.5, 61.6 (C-6′, C-6″), 99.9, 100.0, 110.4, 110.5 (4×*C*CH_3), 112.× (C-3), 153.1 (C-4); HRMS (FAB) Found: M^++1, 571.24946. $C_{20}H_{39}N_2O_{12}$ requires 571.25030.

3.6. Preparation of 3,4-di(β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (16)

A solution of 3,4-di(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (**8**) (30 mg, 0.04 mmol) in methanol (10 ml) was treated with a saturated ammonia solution in methanol (10 ml). After stirring overnight TLC indicated the absence of starting material and formation a more polar product. The reaction mixture was concentrated in vacuo and co-evaporated with methanol (3×10 ml) to afford 3,4-di-(β-D-glucopyranosyl)-1,2,5-oxadiazole 2-oxide (**16**) as an oil (15 mg, 91%); $[\alpha]_D^{18}$=+35.7 (c=0.14, H_2O); δ_H (250 MHz, D_2O) 3.36–3.70, 3.83–4.01 (12H, 2m, 2′-H, 3′-H, 4′-H, 5′-H, 6′a-H, 6′b-H, 2″H, 3″-H, 4″-H, 5″-H, 6″a-H, 6″b-H), 4.56, 4.60 (2H, 2d, $J_{1'-2'}$=10.0 Hz, $J_{1''-2''}$=10.0 Hz, 1′-H, 1″-H); δ_C (90 MHz, D_2O) 61.4, 61.4 (C-6′, C-6″), 69.9, 70.0, 70.7, 71.8, 72.5, 74.5, 77.2, 77.2, 80.9, 81.1 (C-1′–C5′, C-1″–C-5″), 115.4 (C-3), 156.0 (C-4); *m/z* (FAB) Found: M^++1, 411.12501. $C_{14}H_{23}N_2O_{12}$ requires M^++1 411.12510.

3.7. Crystal structure of furoxan 7

Diffraction data were collected with graphite-monochromated Cu Kα radiation (λ=1.54184 Å) on a Stoe Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device operating at 150 K. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (Shelxtl).[27] The 2-oxide substituent of the 1,2,5-oxadiazole ring is disordered over the 2- and 5-positions in the ratio 0.85:0.15(2). All non-H atoms except for the minor component O-atom were refined with anisotropic displacement parameters; H-atoms were placed in idealised positions. Crystal data: $C_{30}H_{38}N_2O_{20}$, M=746.62, triclinic, a=7.839(3), b=8.6191(18), c=13.229(3) Å, α=97.803(11)°, β=97.599(16)°, γ=91.07(2)°, V=877.2(4) Å^3, space group $P1$ (the compound was known to be chiral); T=150 K, Z=1, D_c=1.413 Mgm^{-3}, colourless block, 0.38×0.20×0.20 mm^3. The final conventional R-factor (based on F and 2694 data with $F>4\sigma(F)$ was 6.71%; w$R2$ (based on F^2 and all 3093 data used in refinement) was 18.37%. The final difference map extremes were 0.44 and −0.37e Å^{-3}. The Flack parameter[28] was 0.1(3); this means that the diffraction data do not establish the 'hand' of the structure, although this is unambiguous from the synthetic route used.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number 186410. Copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033 or email: deposit@ccdc.cam.ac.uk).

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